RESQCPR SYSTEM

Sponsor Executive Summary

P110024

Circulatory System Devices Panel Meeting
May 6, 2014

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

1 SYNOPSIS

1.1 Disease Background

Cardiac arrest remains a leading cause of death, currently affecting >250,000 Americans outside the hospital and a similar number inside the hospital annually. It affects the young and the old, often prematurely terminating life in its prime. Nearly two-thirds of all patients who suffer from sudden cardiac death are male and their average age is approximately 65 years old. The average age of survivors is approximately 55 years old. Survival rates from this major health epidemic have remained largely unchanged for decades.[1,2]

1.2 Current Standard of Care, Unmet Need

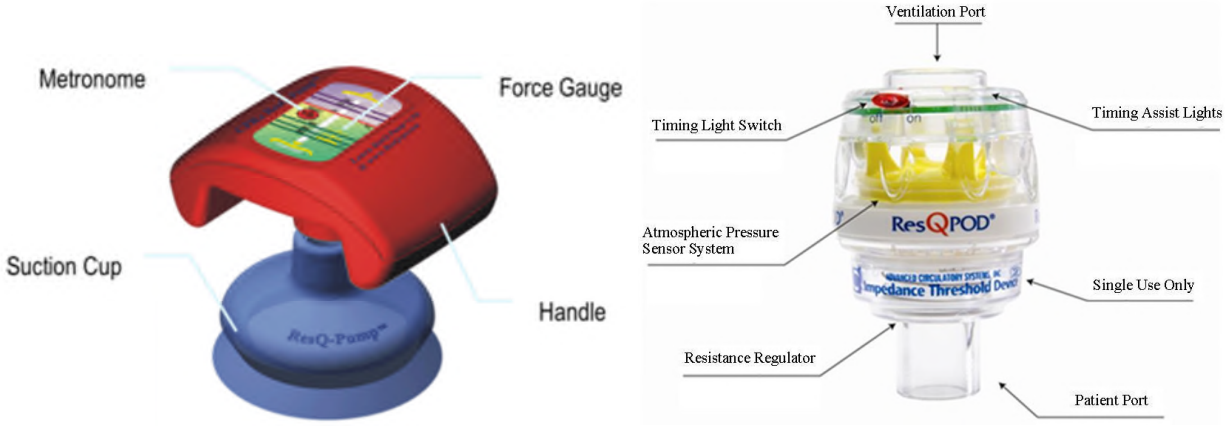
As recommended by the American Heart Association (AHA), the current standard of care for patients with an out-of-hospital cardiac arrest (OHCA) includes manual cardiopulmonary resuscitation (CPR) delivered at a rate of ≥100 compressions per minute with a depth of 2 inches.[3] Periodic positive pressure ventilations are recommended to assure adequate oxygenation and periodic inflation of the lungs. This method of CPR has been shown in animals to provide 15-30 % of normal blood flow to the heart and brain.[4,5] Although closed-chest manual standard CPR (S-CPR) was initially described more than 50 years ago, survival rates remain low. Nationally, survival with favorable neurological function for all patients following OHCA and treated with S-CPR averages <6% (ranging from <1% to 20% nationwide). The ResQCPR System is intended to help address this major public health problem. Specifically, it is intended to provide greater circulation to the heart and brain than S-CPR, thereby increasing the likelihood of survival to hospital discharge with a favorable neurological outcome.[6-8]

1.3 Device Description

The ResQCPR System is intended for use in the performance of CPR to increase survival with favorable neurological function in patients with non-traumatic cardiac arrest.

The ResQCPR System consists of two components: the ResQPump Active Compression Decompression (ACD) CPR device and the ResQPOD Impedance Threshold Device (ITD) 16.0.

Figure 1.1 ResQPUMP and ResQPOD



The ResQPUMP is a hand-held ACD device that can be placed on the patient's chest and secured by a suction cup. The rescuer manually pushes down and pulls up on the device handle to perform CPR. The ResQPUMP is designed to transform the patient's chest into an active bellows but does not, in itself, generate significant negative intrathoracic pressure during the active chest decompression phase. The ResQPOD ITD is a valve system that fits onto a rescue face mask or breathing tube. It does not restrict the patient's ability to exhale, nor the rescuer's ability to ventilate. It acts to impede inspiratory gas exchange during the chest recoil or decompression phase of CPR thereby lowering airway pressure and intrathoracic pressure. This intrathoracic vacuum helps to refill the heart with blood after each compression. The decrease in intrathoracic pressure also lowers intracranial pressure during the decompression phase, thereby lowering resistance to forward cerebral blood flow.

In addition, the device combination provides the user with visual and auditory guides to help perform CPR correctly. The ResQPUMP includes an audible metronome to guide the compression rate and a force gauge to guide compression depth and active chest decompression. Timing lights on the ResQPOD flash 10 times per minute to guide the ventilation rate.

1.4 Pivotal Study Design and Conduct

The ResQTrial was an NIH-funded pivotal, multicenter, prospective randomized clinical trial. It was performed in seven US geographical sites in conjunction with 49 Emergency Medical Service (EMS) agencies and 40 hospitals from 2005 to 2010. The study tested the hypothesis that use of the ResQCPR System would result in a significant increase in survival to hospital discharge with a favorable neurologic outcome versus S-CPR alone in adults after out-of-hospital cardiac arrest of presumed cardiac etiology.

Subjects were randomly assigned to receive S-CPR or ResQCPR. The study protocol was approved by the FDA, the NIH, and 26 participating Institutional Review Boards (IRBs). The hypothesis evaluates the potential synergistic benefit of the ResQPOD and ResQPUMP in combination as the ResQCPR System, not the potential benefit of either device alone. A third arm, S-CPR+ the ResQPOD alone, was planned but the Company recognized early in the pivotal study that resources would be limited. Therefore, at the recommendation of the Data Safety

Monitoring Board, (DSMB) the Company discontinued that third arm so that it could focus those limited resources on the primary study objective, the comparison between S-CPR and ResQCPR.

Subjects were enrolled in the ResQTrial if they had an OHCA and received CPR by EMS personnel. All enrolled subjects were ≥18 years of age. Enrollment started at each site with a randomized run-in phase conducted in an identical manner to the pivotal phase. Once a site demonstrated proficiency in the run-in phase, the pivotal phase was initiated at the site. Consent to continue participation was required for all patients admitted to the hospital. All subjects who survived to hospital discharge had follow-up assessments at the time of hospital discharge and then at 30, 90, and 365 days after the cardiac arrest.

The intention-to treat (ITT) population included adults (≥18 yrs) with non-traumatic out-of-hospital cardiac arrest (OHCA). It is well established that subjects in cardiac arrest represent a heterogeneous population: some individuals are known to respond well to CPR while others respond poorly to CPR with little or no likelihood of survival with any treatment.[3,9] Therefore, analysis of the ResQTrial results focused on subjects who generally have the capacity to benefit from CPR, which is why the study used a modified intention-to treat analysis (mITT) for primary analysis. Subjects were included in the mITT population if they had an OHCA of presumed cardiac etiology. The mITT population excluded subjects who were determined to have had a cardiac arrest secondary to a non-cardiac etiology such as a respiratory cause (e.g., pulmonary embolism), hemorrhage, stroke, metabolic abnormality (e.g., hyperkalemia), drug overdose, or electrocution. Subjects with the following conditions were also excluded from the mITT population: CPR provided by EMS personnel for < 1 minute; complete airway obstruction that could not be cleared or attempts at advanced airway management were unsuccessful; intubation with a leaky or uncuffed advanced airway device; or a stoma, tracheotomy, or tracheostomy.

The primary composite safety and effectiveness endpoint was survival to hospital discharge with favorable neurological function, as determined by the modified Rankin Scale (mRS) scoring system, for all subjects in the mITT analysis population.

The secondary safety endpoint was the rate of major adverse events associated with the ResQCPR System. Major adverse events included death, rib or sternal fractures, pulmonary edema, and internal organ damage. The major adverse event rate for patients receiving ResQCPR was hypothesized to be equivalent to that for patients receiving S-CPR. The secondary effectiveness endpoint was long term neurological survival, assessed 90 days and 1 year after OHCA in subjects who survived to hospital discharge using the Cognitive Abilities Screening Instrument (CASI).

Additional secondary endpoints included survival status and neurological function 30, 90, and 365 days after the cardiac arrest with subgroup analyses based upon gender, age, first recorded rhythm, site, 911 call-to-EMS CPR <10 and >10 minutes, and witnessed status as well as short- and long-term survival and neurological function outcomes for the entire ITT subject population, run-in phase outcomes, and a per protocol analysis if there were randomization errors.

1.5 Pivotal Study Statistical Analysis

The primary endpoint (survival to hospital discharge with a favorable neurologic outcome) in the study arms was evaluated at the time of a pre-planned interim analysis (50% of enrollment) and the final analysis (100% of enrollment). Based upon historical control data from participating sites, it was assumed for purposes of sample size calculation prior to initiation of the study that survival to hospital discharge in the control (S-CPR) arm would be 6% with a detectable improvement expected in the investigational (ResQCPR) treatment arm to 10.2% and an odds ratio of 1.77. A total sample size of 1,400 evaluable subjects was proposed for the study, with 700 subjects randomized to each of the two treatment arms. An interim analysis was performed to potentially adjust sample size upward but not to stop the study early based on favorable results. A two-sided alpha of 0.022 was initially specified for the study before a third study arm (S-CPR+ResQPOD) was discontinued as described below in **Section 1.6.2**. In order to continue to maintain an overall error level of 0.049 after the discontinuation of the third study arm, the significance level was changed to 0.049 (Lan-DeMets group sequential alpha spending levels). The FDA approved this change to the Statistical Analysis Plan in 2008.

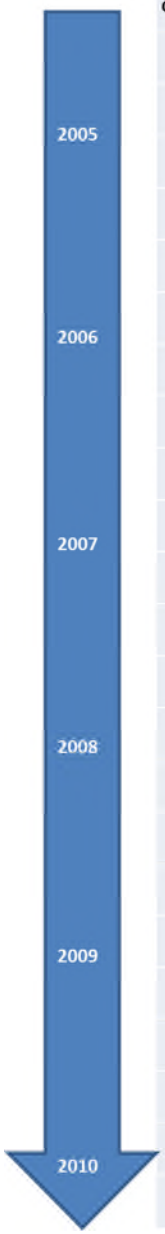
Subjects from the run-in phase were not included in the primary endpoint analysis. The primary data analysis was based on the randomization assignment for those subjects who met the pre-specified final criteria for the mITT population.

1.6 Pivotal Study Implementation

1.6.1 Study Performance and Timeline

A study timeline, shown in **Figure 1.2**, provides the dates of the key events that took place during the course of the study. Enrollment is shown on a quarterly basis and the cumulative number of subjects enrolled who met criteria for mITT analysis at the end of each quarter are shown in parentheses.

Figure 1.2 Chronology of Study Events



Quarter (mITT enrollment)	KEY EVENT
Q1 (0)	Initial NIH funding awarded
Q2 (0)	FDA approved IDE for enrollment of 1,400 subjects
Q3 (0)	
Q4 (0)	Sites enrolled first run-in phase subject
Q1 (11)	Sites enrolled first pivotal phase subject
Q2 (80)	FDA approved inclusion of medication/drug overdoses in mITT
Q3 (158)	
Q4 (240)	
Q1 (342)	
Q2 (418)	
Q3 (505)	3rd study arm (S-CPR + ResQPOD alone) was discontinued
Q4 (623)	Site 6 began pivotal phase enrollment
Q1 (784)	Additional NIH funding awarded
Q2 (942)	
Q3 (1071)	Study was resized to enrollment of 1348 subjects per study arm based on DSMB recommendation after interim analysis was performed per protocol,
Q4 (1247)	FDA guidance *Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials* released
Q1 (1420)	Implementation of updated FDA 50.24 guidance began
Q2 (1608)	Site 7 began pivotal phase enrollment
Q3 (1655)	DSMB was unblinded, new NIH application not funded and new subject enrollment was suspended
Q4 (1655)	
Q1 (1655)	Second new NIH application not funded and new subject enrollment was permanently stopped
Q2 (1655)	
Q3 (1655)	1 year follow-up on all subjects was completed and Sponsor was unblinded

The initial NIH grant for the ResQTrial was awarded in February 2005, the first subject was enrolled in the run-in phase in October 2005, and the one year follow-up on the last subject enrolled was completed in July 2010. The study protocol was carefully and thoroughly implemented by the site investigators and their staff, though some aspects of the study logistics were formidable. For example, ResQCPR devices were placed onto and removed from hundreds of EMS rigs hundreds of times each based upon a block weekly randomization schedule. In addition, during the course of the study, more than 4900 EMS personnel were trained on how to perform S-CPR and ResQCPR.

1.6.2 Study Design Changes

Discontinuation of the Third Study Arm

As noted above, the Company recognized early in the pivotal study that resources would be limited and, therefore, discontinued the third study arm, S-CPR+ ResQPOD alone, so that it could focus those limited resources on the primary study objective, the comparison between S-CPR and ResQCPR. The Company and DSMB were blinded to study results of the third arm when the recommendation was made by the DSMB to discontinue enrollment in that arm in September 2007. FDA approved the discontinuation of the third study arm at that time.

Resizing of the Study after the Interim Analysis

The original study plan called for 700 mITT subjects per treatment arm in the pivotal phase. A single pre-planned midpoint interim analysis after enrolling 350 mITT subjects per arm in March 2008 showed that there was a relative 50% difference in outcomes between groups (masked as Group A and Group B). It should be noted that the DSMB was blinded to the results by treatment group at this time, and the direction of the difference between treatment groups was unknown. Based upon this interim analysis, the DSMB recommended that the sample size be increased to 1,348 subjects per arm to maintain a statistical power of 0.8. Two additional study sites were added to increase the enrollment rate. The seventh and last study site began enrollment in the pivotal phase in April 2009.

Early Study Termination

Efforts to obtain continued funding from NIH to enroll the full 1,348 subjects per study arm were undertaken but did not result in additional funding. In July 2009, the DSMB recommended that new subject enrollment be curtailed if there was insufficient funding to enroll the proposed full number of additional subjects so as to not unnecessarily involve subjects in an investigational research study that could not be fully funded. The study was finally terminated due to this lack of funding in July 2010, with completion of the final subject follow-up. Compliance was maintained with all study protocol requirements, and a total of 1,655 mITT subjects were ultimately enrolled by the time of study discontinuation. The Company continued to remain blinded to aggregate study results by treatment group at the time the study was terminated.

1.6.3 Informed Consent Process

The study was performed under 21 CFR § 50.24: *Exception from informed consent for emergency research*. This regulation allows an IRB to authorize an investigation without prior informed consent for subjects in certain life-threatening situations where the investigation would be impossible without such a waiver. For the first time, these regulations provided the opportunity to evaluate new CPR devices but also presented some practical challenges. Before enrolling subjects, investigators obtained permission from all 26 local Institutional Review Boards to initiate the study. Additionally, investigators fulfilled comprehensive community consultation and notification requirements outlined in the regulation. This included meeting with hundreds of interested individuals in multiple public forums throughout the geographical area where the study would be conducted. At these meetings, the rationale for the study was presented and discussed and the study protocol was reviewed. Public notification that the study would be

performed was provided in are newspapers, radio, and television spots. All EMS agencies had to demonstrate they were in compliance with Federalwide Assurance for the Protection of Human Subjects. Once the study was initiated, all subjects and/or their legally authorized representative (LAR) were approached by study personnel after subjects were admitted to the hospital to obtain consent to continue participation in the study and to track the subject's short- and long-term outcomes.

In October 2008, nearly three years after the first subjects were enrolled in the ResQTrial, FDA issued a new guidance document (*Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials*), clarifying circumstances under which data could be obtained in emergency consent situations where informed consent was neither obtained nor denied.[10] Prior to release of this new guidance, the local IRBs' interpretation of existing regulations did not allow investigators to gather any data from the subjects' medical records in the absence of consent. As such, lack of consent prevented review of many medical records. Moreover, consent was most commonly denied in subjects who had a poor neurological prognosis. Following release of this guidance document, investigators petitioned their respective IRBs for permission to review subjects' medical record when consent was neither obtained nor declined or up to the point in time consent was denied in all subjects enrolled in the ResQTrial, in order to assess the primary endpoint. In certain cases, the FDA's 2008 guidance provided the opportunity for investigators to obtain additional clinical information that led to the correction of the initial cohort assignment (e.g., from ITT to mITT or vice versa) at a considerable time interval after an individual patient's OHCA (e.g., subjects enrolled in 2006 for which consent could not be obtained prior to publication of the guidance). Ultimately, the Company was able to evaluate the primary study endpoint in 99% of the primary analysis population.

1.6.4 Study Blinding

Blinding could not be accomplished at the point of care due to the nature of the study and devices. However, individuals who performed the neurological assessments were blinded to the method of CPR used, as were individuals caring for the subjects in the hospital. Study personnel monitoring the study were not blinded to the method of CPR on individual CRFs so they could assess device implementation, possible device malfunction, randomization errors, and document adverse events. All study personnel, however, both study site and Company personnel, as well as all members of the Clinical Events Committee (CEC), remained blinded to aggregate data based on treatment received until July 2010, after the final enrolled subject surviving to one year was assessed. More specifically, treatment groups were masked as Group A and Group B prior to unblinding with no indication as to the identity of the specific groups. The Company received copies of the DSMB reports that included masked Group A and Group B data and provided these reports to FDA on an annual basis. The DSMB requested to become unblinded to the identity of the specific groups in July 2009; this request to become unblinded was unknown to the Company and all other study personnel. An independent biostatistician was the only individual who was unblinded to aggregate study outcomes throughout the trial.

The FDA raised a potential issue in September 2012 during a FDA inspection, two years after the completion of the study and one year after the submission of the PMA, that the Company

could have become unblinded to treatment-group specific aggregate data during the study by comparing data from interim DSMB study reports with data from interim DSMB quality assurance reports. All parties involved in the study (Company, DSMB, independent biostatistician) were surprised to learn about this possibility during the inspection and have affirmed that they were unaware of this potential for unblinding through the combination of reports.

The Company maintains that it has always been transparent with FDA and had submitted all DSMB study reports and quality assurance reports, as well as Annual Reports, to the Review Branch in CDRH/ODE on an annual basis during the study. Further, the Company maintains that it remained blinded to treatment-group specific aggregate data during the entire enrollment and follow-up phase of the study.

1.6.5 CEC and DSMB Functions

An independent Clinical Event Committee (CEC) and Data Safety Monitoring Board (DSMB) were important organizational units that strengthened the conduct of the study. During the course of the study, the independent CEC convened multiple times, reviewed all adverse events, and determined, in a blinded manner, whether cases selected by the site investigators for review met criteria for the mITT analysis population. An independent DSMB was also convened on several occasions. The DSMB included a member specifically appointed by NIH. The DSMB reviewed all aggregate data in a blinded manner (Group A vs. Group B) and CPR quality assurance data in an unblinded manner to assure the study was performed in the best interests of the public and the subjects and to provide recommendations on whether or not to continue subject enrollment. The DSMB also made recommendations to the Sponsor regarding the continuation and sizing of the study.

1.7 Pivotal Study Results

A total of 1,655 subjects with an OHCA of presumed cardiac etiology who were enrolled in the ResQTrial pivotal phase met the criteria for the mITT analysis population; 110 (6.6 %) were alive and available for analysis of CPC score at completion of the study (one year follow-up). Subject demographics and baseline characteristics for the mITT population were similar between the two study arms.

The study demonstrated a statistically significant 52% relative improvement in patients surviving with favorable neurological outcome in the ResQCPR group compared with S-CPR, as well as a significant 44% and 49% increase in survival to 90 and 365 days, respectively, after OHCA. There was no difference in the overall major adverse event rates between the study groups.

1.7.1 Primary Effectiveness and Safety Endpoint

Analysis of the primary composite effectiveness and safety endpoint was based on the 1,655 evaluable subjects in the mITT population. As shown in **Table 1.1**, there was a relative 52% increase in the number of subjects who survived to hospital discharge with a favorable neurological outcome in the ResQCPR group compared with S-CPR: 8.9% (75/838) vs. 5.9%

(47/800), p=0.019, OR 1.58 [CI= 1.06, 2.35]. Therefore, the study met the primary endpoint. In addition, the distribution of neurological function of survivors at the time of hospital discharge was significantly improved in the ResQCPR treatment group versus controls: more subjects had normal or near normal neurological function, as shown by the distributions of subjects with lower mRS scores (p=0.037).

Table 1.1 Primary Effectiveness and Safety Endpoint Results (mITT)

	S-CPR (N=813)	ResQCPR (N=842)	p-value
mRS≤3 (primary study endpoint)	**47 (5.9%)**	**75 (8.9%)**	**0.019**
mRS at hospital discharge[1]			
mRS 0	3	11	0.037
mRS 1	8	11	
mRS 2	26	30	
mRS 3	10	23	
mRS 4	10	10	
mRS 5	16	18	
mRS 6 (death)	727	735	
Survival data for hospital discharge not available	6	2	
Survived, mRS not available	7	2	

Data expressed as number (%) or mean (SD) unless otherwise stated and include all patients who met final study mITT analysis population criteria

[1]For mRS scores, 0 is asymptomatic, 1 is no significant disability, 2 is slight disability, 3 is moderate disability, 4 is moderately severe disability, 5 is severe disability, and 6 is dead

1.7.2 Analysis of All Subjects Enrolled in the Pivotal Phase (ITT Population)

An analysis of all OHCA subjects randomized and treated in the pivotal phase of the ResQTrial with known primary endpoint data (the ITT population) revealed that 71/1186 (6.0%) treated with S-CPR survived to hospital discharge with a mRS ≤3 compared with 101/1262 (8.0%) in the ResQCPR group (OR 1.37; 95% CI [0.99, 1.90]; p=0.057). This larger ITT population also included initially enrolled individuals who were later determined to have documented etiologies of non-cardiac origin and who were less likely to benefit from any type of CPR administered. The ITT population is representative of the anticipated post-market use of the ResQCPR System and is immune to many of the challenges associated with the study (potential for unblinding, timing of data flow, etc.). For these reasons, it is important to consider the 33% relative increase in survival to hospital discharge with favorable neurologic outcomes with the ResQCPR System in the ITT analysis population when evaluating the effectiveness of the ResQCPR System and the robustness of the successful mITT primary endpoint analysis.

1.7.3 Secondary Effectiveness Endpoint

There was a statistically significant 44% increase in survival to 90 days and 49% increase in survival to 365 days after OHCA in the ResQCPR treatment arm compared with S-CPR (p = 0.024 and 0.030, respectively).The pre-specified secondary effectiveness endpoint was an evaluation of long-term neurological function for subjects in the mITT population. Mean 90 and 365 day CASI scores were not significantly different among survivors who were discharged

from the hospital (p=0.549 and 0.100, respectively) as hypothesized. These mean scores (**Table 1.2**) included subjects who died after hospital discharge, with a CASI score equal to 0 assigned to those who died. More than 85% of the one year survivors in both study arms completed the one year CASI assessment. The mean ± S.D. CASI scores for these subjects were 93.7 ± 11.8 (n=30) in the S-CPR arm and 94.7 ± 4.4 (n=41) in the ResQCPR arm (p=0.68), consistent with full or nearly full recovery in both groups. There were only three patients with CASI scores <70, a score consistent with poor neurological function, in both groups. These results are important clinically as they indicate that: 1) there were significantly more long-term survivors with ResQCPR treatment, 2) when compared with S-CPR, ResQCPR did not increase the number of long-term survivors with severe neurologic deficits and 3) nearly all survivors in both groups had normal or almost normal cognitive function by one year after OHCA.

Table 1.2 Secondary Effectiveness Endpoint Results (mITT)

	S-CPR (N=813)	ResQCPR (N=842)	p-value*
Survival to 90 days	58 (7.3%)	87 (10.5%)	0.024
Not available	15	9	
CASI[1] (mean ± SD) at 90 days	69.86 ± 41.68	74.38 ± 37.48	0.549
Survival to 1 year	48 (6.0%)	74 (9.0%)	0.03
Not available	19	20	
CASI (mean ± SD) at 365 days	57.39 ± 47.04	71.89 ± 41.04	0.100

Data expressed as number (%) or mean (SD) unless otherwise stated and include all patients who met final study mITT analysis population criteria.

* The p-values for survival to 90 days and 1 year are unadjusted.

[1]Cognitive Abilities Screening Instrument (CASI) assessed attention and short-term memory, long-term memory, judgment, spatial ability, and concentration on a scale of 0-100 in which 100 is a perfect score. Subjects who survived to hospital discharge but died prior to 90 day or 1 year follow-up had a CASI score of 0 imputed in accordance with the study analysis plan.

1.7.4 Subgroup Analyses of mITT Population

The positive results for the primary outcome (survival to hospital discharge with a favorable neurological outcome) were consistent throughout the pre-specified subgroup analyses based upon age, gender, witnessed status, time from 911-EMS CPR <10 minutes, study site, and first recorded rhythm of ventricular fibrillation. Subjects with a witnessed arrest treated with ResQCPR had a significantly higher likelihood of survival with a mRS ≤3 than those in the control group (OR 1.56, CI [1.03, 2.37]).

1.7.5 Per Protocol and As-Treated Analyses

The SAP specified that a 'per protocol' analysis would be performed in the mITT population if randomization errors were present in the study. Based on this, a 'per protocol' analysis was performed limited to subjects who met the final enrollment criteria, provided mRS evaluations, and had no protocol deviations relating to the delivery of CPR treatment (i.e., randomization errors). The resulting success rates in the 'per protocol' population based upon randomization errors were estimated to be 8.8% in the ResQCPR group vs. 5.9% in the S-CPR group (p=0.034).

After completion of the study and submission of the PMA, the FDA decided that it would assess the robustness of the primary effectiveness results through the use of post-hoc 'treatment-method delivered' analyses. A limitation of these analyses is that they result in the potential for some subjects with the highest likelihood of survival and a successful outcome (i.e., those that were randomized to the device group but resuscitated before the device could be applied) to be re-classified from the ResQCPR group to the standard CPR group but not the reverse, introducing a one-directional bias in favor of standard CPR. Despite this one-directional bias, these as-treated analyses consistently demonstrated higher survival to hospital discharge with favorable neurological outcome rates in the ResQCPR group.

1.7.6 Impact of Unobtainable Data in 17 Subjects

There were 17 subjects in the mITT population with unobtainable mRS values in the primary analysis population (approximately 1.0% of the total mITT population of 1,655). When values were imputed using the observed mRS results by study group in subjects who were admitted to the hospital, the success rate was estimated to be 9.0% in the ResQCPR group vs. 6.2% in the S-CPR group (p=0.033). A second imputation that was based upon predictive modeling with baseline covariates gave similar results favoring ResQCPR (8.9% vs. 5.9%; p = 0.024).

In addition, a tipping point analysis demonstrated that a loss of statistical significance for the comparison of the primary endpoint between study groups would occur if 5 subjects without endpoint success were removed from the ResQCPR group (p=0.055) (at this tipping point, there would be 23 more subjects who survived with favorable neurologic outcome and a 42% relative increase in survival with good neurologic function in the ResQCPR group).

1.7.7 Timing of Data Collection and Flow

The unique challenges of conducting out of hospital sudden cardiac arrest research presented four circumstances that could have affected the timeline of data flow in the study: 1) implementation of FDA's 2008 Exception from Informed Consent Requirements for Emergency Research guidance, 2) an interim DSMB review occurring before all cases had been adjudicated by the CEC, 3) not all data for an enrolled subject being available at the time of an interim DSMB review, or 4) monitoring activities that were ongoing through the end of the study. These circumstances created the potential for collection of additional information that changed the mITT assignment and/or mRS score for certain subjects during the study, sometimes months or years after the patient's initial enrollment. These changes were made in a uniform manner for all study subjects and study groups and were consistent with FDA guidance. Post hoc analyses demonstrated that these modifications occurred in only a limited number of subjects and had no significant impact on overall study outcomes.

1.7.8 Secondary Safety Endpoint

The analysis of safety was based on the treated cohort of 1,655 subjects available for evaluation prior to hospital discharge. The safety analysis included major adverse events that were reported from the pre-hospital resuscitation effort up to the point of hospital discharge. There was no difference in the overall major adverse event rates between the study groups (p=0.43). The only

difference in adverse events was an increase in pulmonary edema in the ResQCPR group which did not affect survival to hospital discharge with good neurological function.

1.7.9 Additional Post-Hoc Analyses

Several additional post-hoc analyses have been performed by the Company and the FDA to examine the robustness of the treatment results. These post-hoc analyses are relevant because of the unique nature of conducting research in the out-of-hospital sudden cardiac arrest environment, the heterogeneous composition of the sudden cardiac arrest population, the inclusion/exclusion criteria for the study, and the sensitivity of the statistical results. Further, these post-hoc analyses are pertinent since the post-marketing experience will involve use of the ResQCPR System in all sudden non-traumatic cardiac arrest patients, regardless of the underlying arrest etiology.

These additional post-hoc analyses, conducted by both the Company and the FDA, demonstrate a consistent improvement in outcomes with the use of the ResQCPR System, regardless of the analysis population, subpopulation, or assumptions made in the analyses.

Table 1.3 Summary of Primary Endpoint Outcome by Analysis Population (ITT, mITT)

Analysis population/subgroup	**Primary Endpoint: Survival to Hospital discharge with mRS≤3**		**Results**	**Relative % increase from S-CPR to ResQCPR**
	S-CPR	**ResQCPR**		
Run-In + Pivotal ITT	5.7% (75/1318) Missing: 1.3% (17)	7.9% (110/1396) Missing: 0.5% (7)	p = 0.027	38.6%
Run-In + Pivotal mITT	5.6% (50/899) Missing: 1.4% (13)	9.0% (84/936) Missing: 0.4% (4)	p = 0.005	60.7%
Pivotal ITT	6.0% (71/1186) Missing: 1.2% (15)	8.0% (101/1262) Missing: 0.6% (7)	p = 0.057	33.3%
Pivotal mITT	5.9% (47/800) Missing: 1.6% (13)	8.9% (75/838) Missing: 0.5% (4)	p = 0.019	50.8%
Original Planned Study Enrollment of 1400 Subjects	6.0% (41/684) Missing: 1.3% (9)	8.9% (64/704) Missing: 0.4% (3)	p = 0.033	48.3%
Cui-Hung-Wang Method (to maintain alpha level when sample size is increased)	Z_{CHW} Statistic = 2.18, p = 0.029			
Bootstrap Pivotal mITT	Odds ratio = 1.58, 95% Confidence Interval (1.08, 2.30)			
Imputation of 17 unobtainable mRS scores predicted from known study group	6.2% (50/813) Missing: 0	9.0% (76/842) Missing: 0	p = 0.033	45.2%

Analysis population/subgroup	Primary Endpoint: Survival to Hospital discharge with mRS≤3		Results	Relative % increase from S-CPR to ResQCPR
	S-CPR	ResQCPR		
mRS results in subjects admitted to hospital				
Imputation of 17 unobtainable mRS scores based on predictions from covariates	5.9% (48/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.024	50.8%
Worst case assumption for unobtainable mRS scores of mRS≥4 in both study groups	5.8% (47/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.018	53.4%
Worst case assumption for unobtainable MRS scores of mRS≥4 for ResQCPR and best assumption of mRS≤3 for S-CPR	7.4% (60/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.281	20.3%
Per Protocol	5.9% (47/790)	8.8% (70/800)	p = 0.034	49.2%
Addition of 192 ITT cases of drug overdose / metabolic imbalance to mITT	6.6% (58/877)	9.0% (86/952)	p = 0.056	36.4%
Addition of 163 ITT cases of medication/drug overdose to mITT	6.6% (57/865)	9.0% (84/935)	p = 0.065	36.4%
Removal of 29 mITT cases where 2008 FDA Guidance document applied to obtain mRS	5.7% (45/787)	8.8% (72/822)	p = 0.021	54.4%
Removal of 46 mITT cases where FDA Guidance applied or IRB permission to obtain mRS	5.7% (44/778)	8.7% (71/814)	p = 0.020	52.6%
Addition of 28 ITT cases with delayed CEC adjudication to mITT	6.2% (50/806)	8.8% (76/860)	p = 0.051	41.9%
Treatment Delivered: *S-CPR subjects with 0 devices used* *ResQCPR with ≥ 1 device used*	5.9% (47/790) Missing: 13	8.3% (67/811) Missing: 3	p = 0.080	40.7%

Analysis population/subgroup	Primary Endpoint: Survival to Hospital discharge with mRS≤3		Results	Relative % increase from S-CPR to ResQCPR
	S-CPR	ResQCPR		
Treatment Delivered: S-CPR with 0 devices used ResQCPR with 2 devices used	5.9% (47/790) Missing: 13	8.1% (63/779) Missing: 3	p = 0.113	37.3%
Treatment Delivered: Subjects with 0 devices used Subjects with 2 devices used	6.7% (55/817)	8.0% (63/784)	p = 0.339	19.4%
Kaplan-Meier: Survival through 1 Year for Subjects Discharged Alive (mITT)	0.736 at 1 Year	0.868 at 1 Year	p = 0.033	
Kaplan-Meier: Survival through 1 Year for Subjects Discharged Alive (ITT)	0.712 at 1 Year	0.823 at 1 Year	p = 0.040	

It should be noted that FDA performed a post-hoc evaluation of all study results using an alpha level of 0.022 instead of the FDA-approved alpha level of 0.049. The FDA states that this post-hoc use of a 0.022 alpha level partially addresses concerns the FDA has about possible alpha inflation occurring as a result of the periodic DSMB reviews of the blinded study results, the planned interim analysis and potential unblinding of the Company during the study.

The study protocol did not allow for the DSMB to terminate the study early as a result of the data summaries prepared for DSMB review or at the time of the interim analysis. Further, the Company maintains that it was not unblinded to aggregate data during the study. There cannot be an inflation of the Type I error if there is no opportunity to reject the hypothesis associated with the primary study endpoint.

1.8 Conclusions

The results of the pivotal trial show that the effect of the ResQCPR System on survival to hospital discharge with favorable neurologic function is superior to conventional manual S-CPR, the standard of care for treatment of out-of-hospital cardiac arrest in the United States today. There was a 52% increase in survival to hospital discharge with favorable neurologic function (primary study endpoint) in subjects with an OHCA of presumed cardiac etiology (mITT population) treated with the ResQCPR System (75/838) compared with conventional CPR (47/800) (p=0.019). This represents a major advance in the field of resuscitation.

The study results were robust and internally consistent. One year after OHCA, 49% more subjects were alive in the ResQCPR group and the vast majority of surviving subjects in both treatment groups had excellent neurological function, as determined by cognitive, functional, and

quality of life testing. In addition, subgroup analysis based upon age, gender, first record rhythm, witnessed status, site of arrest, and 911 to EMS CPR time demonstrated a consistent benefit with ResQCPR across subgroups for the primary endpoint. Subjects treated with the ResQCPR System and S-CPR had similar adverse event rates. The ResQCPR System had a similar risk profile to S-CPR.

Given the high prevalence and devastating nature of cardiac arrest, lack of alternative effective therapies, and better efficacy of the ResQCPR System versus the best available standard-of-care CPR technique, the Company believes that the benefits of the ResQCPR device system for the treatment of patients with cardiac arrest significantly outweigh the risks. This conclusion is supported even further by the device system's excellent safety profile and increased survival rate observed for all enrolled subjects treated (ITT population), regardless of the cause of the non-traumatic arrest, with restoration of normal or nearly normal neurologic function.

2 ABBREVIATIONS AND DEFINITIONS

2.1 Abbreviations

ACD-CPR	active compression decompression cardiopulmonary resuscitation
ACSI	Advanced Circulatory Systems, Inc.
AED	automated external defibrillator
AHA	American Heart Association
ALS	advanced life support
BLS	basic life support
CASI	Cognitive Abilities Screening Instrument
CFR	Code of Federal Regulations
cmH_2O	centimeters of water
CEC	Clinical Events Committee
CQI	continuous quality improvement
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
CRF	case report form
DNR	Do Not Resuscitate
DSMB	Data and Safety Monitoring Board
EMS	emergency medical services
EMT	emergency medical technician
ET	endotracheal
$ETCO_2$	end tidal carbon dioxide
FDA	Food and Drug Administration
GCP	good clinical practices
HUI3	Health Utilities Index Mark 3
ICU	intensive care unit
ICD	implantable cardioverter defibrillator
IDE	investigational device exemption
IRB	institutional review board
ITD	impedance threshold device
ITT	intention to treat
MD	medical doctor
mmHg	millimeters of mercury
mRS	Modified Rankin Scale
NIH	National Institutes of Health
OHCA	Out-of-hospital cardiac arrest
OPC	Overall Performance Category
PEA	pulseless electrical activity
PI	principal investigator
PMA	premarket approval
QA	quality assurance
ROSC	return of spontaneous circulation
S-CPR	standard CPR
UADE	unanticipated adverse device effect

2.2 Definitions

Cerebral Performance Category (CPC) – A standardized scale used to assess neurological outcome in subjects surviving to hospital discharge. The 5 CPC categories include:

1. Good Cerebral Performance (conscious, alert, able to lead a normal life),
2. Moderate Cerebral Disability (conscious, sufficient cerebral function for part-time work),
3. Severe Cerebral Disability (conscious, dependent on others for daily support),
4. Coma, Vegetative State (not conscious), and
5. Death (certified brain dead or dead by traditional criteria).

Evaluable Subject – Subject enrolled in the study and who meets final inclusion criteria. These subjects count towards the proposed 1400 target enrollment.

Modified Rankin Scale – A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. Scores are as follows:

0. No symptoms at all
1. No significant disability despite symptoms; able to carry out all usual duties and activities
2. Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3. Moderate disability; requiring some help, but able to walk without assistance
4. Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6. Dead

Overall Performance Category (OPC) – A standardized scale used to assess overall neurological outcome in subjects surviving to hospital discharge. The 5 OPC categories include:

1. Good Overall Performance (healthy, alert, capable of normal life. CPC 1 plus no or only mild functional disability from non-cerebral organ system abnormalities),
2. Moderate Overall Disability from non-cerebral system dysfunction alone or both. Performs independent activities of daily living (dressing, traveling, and food preparation). May be able to work part-time in sheltered environment but disabled for competitive work,
3. Severe Overall Disability (Conscious. Severe cerebral disability alone [CPC 3] or severe disability from non-cerebral organ system dysfunction alone or both. Dependent on others for daily support.),
4. Same as CPC 4, and
5. Same as CPC 5. OPC will also be assessed for all subjects qualifying for CPC classification as outlined above.

Quality of Life Assessment – An assessment of the subject's quality of life using a validated Quality of Life instrument or questionnaire.

Return of Spontaneous Circulation (ROSC) – Any return of spontaneous palpable pulse usually detectable by a major artery in the absence of CPR. This return of palpable pulse does not need to return for any set duration according to the Utstein guidelines.[9]

Survival to 1-Hour – Subject who, at 60 minutes from the time of first ROSC, has a spontaneous palpable pulse and measurable blood pressure, with or without adjunctive therapy, including vasopressors. The subject may or may not be breathing spontaneously and may or may not be intubated. The need for continuous CPR or mechanical CPR devices 1 hour after an initial ROSC implies the absence of spontaneous circulation; and such subjects will not be considered 1-hour survivors. Artificial circulatory assists such as emergency cardiopulmonary bypass and intra-aortic balloon pumps imply that spontaneous circulation is present, and such subjects will be considered 1-hour survivors.

Survival to Admission to an Acute Care Unit – Subject successfully admitted to the hospital's intensive care unit (ICU) with return of spontaneous circulation and measurable blood pressure. ICU admission can occur before or after the use of vasopressors. A subject can be considered admitted even in the absence of spontaneous ventilation and may or may not be intubated. No specified time duration is necessary for successful ICU admission. This definition includes admission to other hospital care units (e.g., hospice, telemetry).

Survival to 24 Hours – Subject who, at 24 hours from hospital admission, has a spontaneous palpable pulse and measurable blood pressure, with or without adjunctive therapy, including vasopressors. The subject may or may not be breathing spontaneously and may or may not be intubated. The need for continuing CPR or mechanical CPR devices implies the absence of spontaneous circulation and such subjects will not be considered 24-hour survivors. Artificial circulatory assists such as emergency cardiopulmonary bypass and intra-aortic balloon pumps imply that spontaneous circulation is present and such subjects will be considered 24-hour survivors.

Survival to Hospital Discharge – Subject who is discharged from the hospital alive.

Survival at 30 Days – Alive on day 30 after the initial (index) cardiac arrest. Subjects who experience additional out-of-hospital cardiac arrest within this period will only be counted once in the study. Thus, survival or death status from a second cardiac arrest within the 30 days after the index event will be assigned to the original event.

Survival at 90 Days – Alive on day 90 after the initial (index) cardiac arrest. Subjects who experience additional out-of-hospital cardiac arrest within this period will only be counted once in the study. Thus, survival or death status from a second cardiac arrest within the 90 days after the index event will be assigned to the original event

Survival at 365 Days – Alive on day 365 after the initial (index) cardiac arrest. Subjects who experience additional cardiac arrest during this period will only be counted once in the study. Thus, a second cardiac arrest within the 365 days after the index event will be assigned to the original event.

3 DISEASE BACKGROUND

3.1 Background

When the heart stops during a cardiac arrest, blood flow to the heart and the brain ceases immediately. Within minutes, energy stores within the heart, brain, and other vital organs become depleted. Without restoration of blood flow, the body dies. The purpose of CPR is to restore and maintain flow of oxygenated blood to the heart and brain, restore vital organ metabolism and function, and facilitate restoration of a stable blood pressure and pulse.

There can be multiple causes for a cardiac arrest. Those of presumed cardiac etiology benefit most from the vital organ perfusion provided by CPR. These causes include an acute occlusion of a coronary artery which triggers ventricular fibrillation, development of ventricular tachycardia or fibrillation often secondary to a scar from prior damage to the heart, a genetic defect that predisposes the heart to ventricular arrhythmias, or a diseased electrical system resulting in the sudden absence of a heartbeat. An exacerbation of pre-existing heart failure can also result in a cardiac arrest. Cardiac arrest can also be secondary to non-cardiac causes including pulmonary embolism, metabolic abnormality, sepsis, hypovolemia, respiratory compromise with profound hypoxemia, and drug overdose. It can often be difficult to discern the cause of the cardiac arrest at the scene in any given patient. Studies have shown that upwards of one-third of patients thought to be in cardiac arrest of presumed cardiac etiology at the scene turn out to have a non-cardiac etiology.[11]

Nationally, survival with favorable neurological function for all patients following OHCA and treated with S-CPR averages <6% (range from <1% to 20% nationwide). Survival after cardiac arrest is highly dependent upon many factors including the cause of the cardiac arrest itself. When the underlying cause of the cardiac arrest cannot be effectively treated by increased circulation and/or defibrillation, long-term survival with favorable neurological function is less unlikely. Patients who present with a first recorded rhythm of ventricular fibrillation have the highest likelihood of survival from cardiac arrest.[12] Those who present with pulseless electrical activity (formerly known as electromechanical dissociation) or asystole (no electrical activity) have a much lower likelihood of survival.

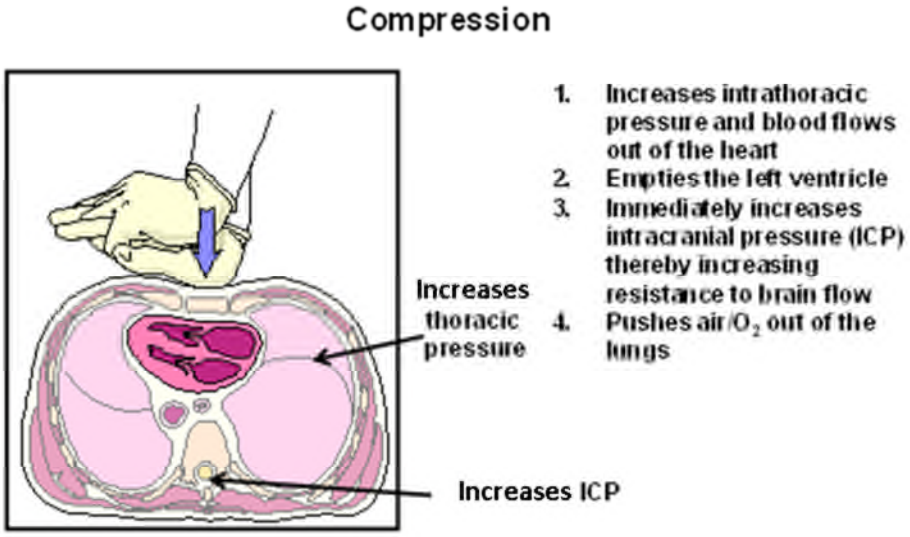
Animal and human data support the concept that a cardiac arrest due to ventricular fibrillation can be treated during the first several minutes (0-4 minutes) after cardiac arrest with a defibrillator.[13-15] This is the so-called 'electrical' phase where restoration to full life is possible without CPR. During the 'circulatory phase', which occurs between approximately 4-8 minutes after arrest, CPR is usually required for successful resuscitation. With each passing minute of untreated cardiac arrest, treatment with CPR and a defibrillator becomes less and less effective. If CPR is not started within 10 minutes after cardiac arrest, few patients survive.

3.2 Physiology of Conventional Manual Closed-Chest CPR

The essential mechanical elements of conventional closed-chest or standard CPR (S-CPR) required to deliver oxygenated blood to the heart and brain can be divided into three components: (1) chest compression, (2) chest decompression, and (3) ventilation. The

physiological impact of each of these components has been studied in animals and humans.[3] During S-CPR, chest compressions are performed with a pair of hands at a rate of 100 per minute; compressions should be 5 cm in depth. With each chest compression, intrathoracic pressure is increased and the heart is squeezed between the sternum and the spine. As shown in **Figure 3.1**, chest compressions during conventional CPR provide the driving force to propel blood forward. Blood flows forward from the non-beating heart towards the brain, coronary arteries, and the rest of the body due to the presence of the one-way cardiac valves and pressure differences between the thorax and non-thoracic structures. During the compression phase, intracranial pressure (ICP) is also increased, which increases resistance to cerebral perfusion, as pressure is transmitted through the para-vertebral venous plexus and spinal fluid to the cranium.[16] Hindrances to optimal performance of S-CPR are common.[17-20] When the chest is compressed too slowly, too rapidly, too much, or too little, blood flow to the brain and heart is reduced when compared with high quality CPR.[3] Interruptions in chest compressions are similarly harmful: without chest compressions, there is no forward blood flow. These issues during CPR can adversely affect outcomes. Attention to detail is essential in order to provide this life-saving therapy correctly.

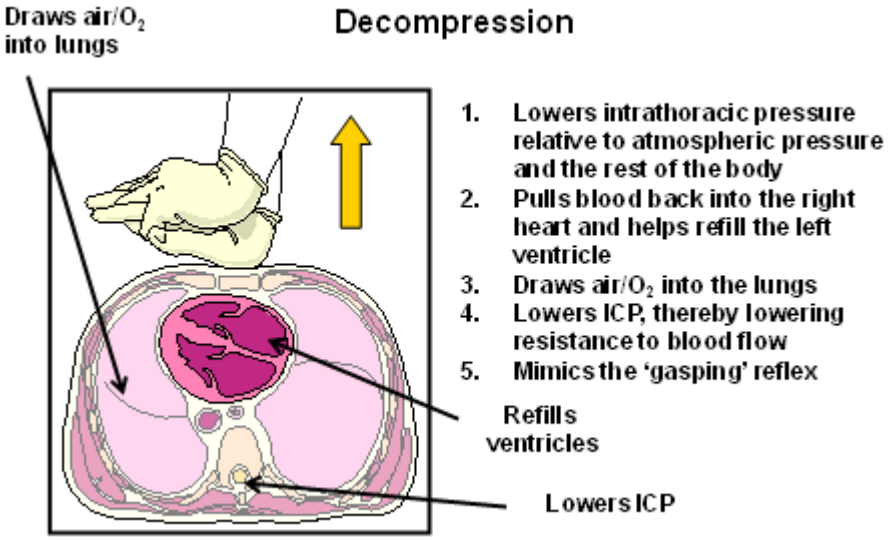
Figure 3.1 Physiology of Chest Compression during CPR



The physiology during the decompression or chest recoil phase of CPR is also complex, as shown in **Figure 3.2**. The chest needs to fully recoil after each compression during conventional CPR. It is during the decompression phase that the heart is refilled after being emptied with the previous chest compression. The refilling process is inefficient when using a pair of hands to non-invasively allow the chest wall structures to recoil naturally. The slight vacuum generated inside the thorax draws some blood back into the heart but also some air into the lungs. Intracranial pressure is minimally reduced with each chest wall recoil by pressure transference via the same mechanisms that result in an increase in ICP during the compression phase. These changes in ICP during the compression and decompression phases play a key role in the generation of cerebral perfusion.[21] If rescue personnel inadvertently lean on the chest and do not allow the chest to fully recoil after each compression, then intrathoracic pressure remains greater

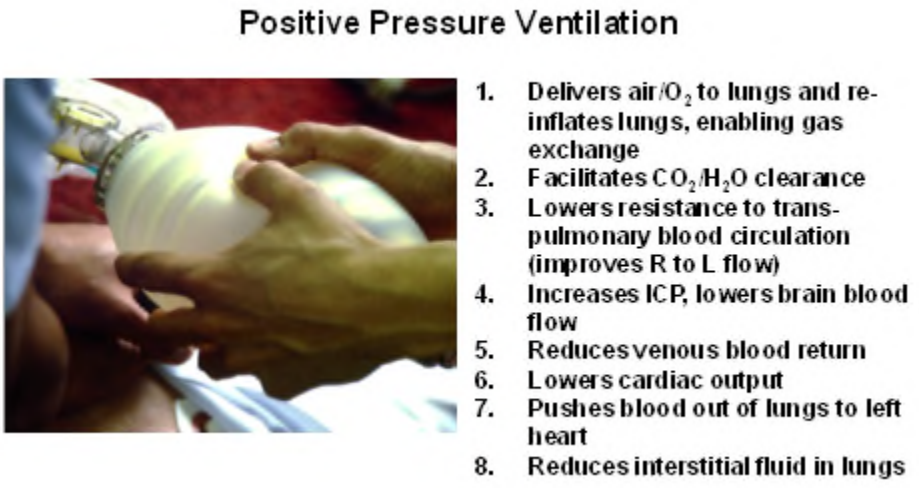
than atmospheric pressure.[22] This common occurrence prevents the refilling of the heart and the reduction in cerebral perfusion, which in turn markedly reduces blood flow to the brain and myocardium.

Figure 3.2 Physiology of Chest Decompression during CPR



Positive pressure ventilation, essential for providing oxygen and removing carbon dioxide during CPR, also affects intrathoracic pressures (**Figure 3.3**). Each positive pressure breath increases intrathoracic pressure which causes a decrease in venous blood flow back to the heart, an increase in ICP, and helps to deliver more blood that is pooled in the lungs to the left heart. Excessive ventilation rates and tidal volumes are associated with a marked decrease in cerebral and myocardial perfusion and increased mortality.[17] After the first few minutes of CPR, in the absence of periodic positive pressure ventilation, blood flow through the lungs is markedly reduced and this results in a profound reduction in cerebral oxygenation and perfusion.[23] The balance between too little and too much ventilation is critical to long-term neurologically-favorable survival after cardiac arrest.

Figure 3.3 Physiology of Ventilation during CPR



In concert, the chest compression and decompression components of manual S-CPR mimic cardiac systole and diastole while the positive pressure ventilation component provides respiratory gas exchange similar to breathing. Further, the gasping reflex observed in some patients in cardiac arrest is associated with a decrease in intrathoracic pressure which causes the entrainment of air into the lungs, venous blood flow back to the heart, and a reduction in ICP.[24] The presence of gasping during CPR is associated with improved outcomes as this brainstem reflex helps to enhance circulation by enhancing venous blood flow back to the heart and reduce ICP and thus increase forward brain blood flow. [24]

3.3 Current Therapies

Manual S-CPR remains the current standard of care for patients in cardiac arrest. A number of devices have been developed to help deliver chest compressions, including several automated compression devices.[25] Some of the automated CPR devices have been studied in large clinical effectiveness trials,[26,27] though none have been shown to provide improved survival to hospital discharge rates when compared with S-CPR. In addition to the automated CPR devices, there are now a number of different devices designed to provide user feedback on the quality of CPR delivered. [28,29] Such devices are currently not in widespread use. Further, none have been shown to provide improved survival to hospital discharge rates when compared with S-CPR. However, these devices can provide user feedback related to the quality of CPR which can help reduce the shortcomings often associated with the delivery of S-CPR.[30]

The ResQPOD ITD 10 is currently available in the United States for home, hospital, clinic and emergency care use, for the temporary increase in blood circulation as directed by a physician or licensed practitioner. It was cleared by FDA in 2003 (K033401). It is contraindicated in dilated cardiomyopathy, congestive heart failure, pulmonary hypertension, aortic stenosis, flail chest, chest pain and shortness of breath. It can be used with a facemask, endotracheal tube or other appropriate airway adjunct used for assisted ventilation. In accordance with the cleared Indications for Use, the ResQPOD ITD 10 is used as a circulatory enhancer in patients undergoing CPR in hospitals and EMS systems. At present, the ResQPUMP is not available in the United States. A device called the CardioPump, which is structurally and functionally

identical to the ResQPUMP, is sold outside the U.S. as an alternative to manual CPR for use in patients in cardiac arrest.

Current methods and devices that provide CPR are most effective when used in combination with other therapies to restore full life such as defibrillation, revascularization, anti-arrhythmic agents, and intensive care unit therapies that support the restoration of circulation and brain function.

3.4 Unmet Clinical Need

All non-invasive CPR methods are intended to circulate enough blood to maintain brain viability and restart the heart. CPR methods that rely on chest compressions must transform the changes in geometry of the thorax during CPR into a means to pump blood. Although S-CPR works, its effectiveness is partly limited due to the lack of adequate blood return to the thorax to refill the heart during the chest wall recoil phase.[31]

The physiological limitations of S-CPR include:

1. Filling of the heart (preload) is dependent upon the chest wall's ability to passively recoil. Inadequate chest wall recoil may occur if: a) the chest is stiff rather than compliant, b) caregivers tire and begin to "lean" on the chest, or c) ribs are broken.

2. With an open airway, air is drawn into the lungs just as the chest wall recoils, thereby preventing the development of negative intrathoracic pressure, the relative vacuum in the thorax responsible for drawing venous blood back to the thorax to refill the heart after each compression. During S-CPR, venous return may be insufficient to maintain sufficient circulation to achieve a restoration of spontaneous circulation, especially over time.

In addition, there are practical limitations with S-CPR:

1. Conventional manual CPR relies upon health care providers to compress the chest, often without any devices to guide them, at the proper rate and depth. Clinical evidence shows that providers have a tendency to compress either too fast or too slow and at the wrong depth without the aid of a metronome and depth gauge. These practical issues may compromise blood flow and survival.

2. Similarly, conventional CPR relies upon health care providers to ventilate, at a correct rate and tidal volume. Without the aid of a metronome and means to deliver a set respiratory volume they may ventilate incorrectly, most typically too fast, creating excessive positive pressure in the chest which diminishes blood flow back to the heart.

When S-CPR is performed correctly, it typically provides only 10 – 20% of normal blood flow to the heart, and 20 – 30% of normal blood flow to the brain.[3] Without adequate circulation, the chances of resuscitating a patient in cardiac arrest are significantly reduced. If CPR is not performed optimally, blood flow to the heart and brain is further reduced, as is the likelihood of a

positive outcome.[17-19,22,23,28,29] Thus, the method of CPR and the way circulation is enhanced is a crucial and fundamental factor in determining who will survive with restoration of full neurologic function after cardiac arrest.

Even with standard of care S-CPR, rates of survival with favorable neurological function remain low (<6%, ranging from <1% to 20% nationwide). New treatments that can increase these rates of survival with favorable neurological function are desperately needed.

The ResQCPR System, as described in detail in the next section, was designed to fulfill this unmet clinical need by providing 2-3 times more circulation to the heart and brain (normal blood flow to the brain and 70% of normal blood flow to the heart, as demonstrated in an animal model) than is possible with S-CPR alone.[7] In addition, the ResQCPR System provides a means to address both the physiological and practical limitations associated with the delivery of S-CPR with features for compressions and ventilations, as well as a depth gauge.

4 DEVICE DESCRIPTION

4.1 Indications for Use

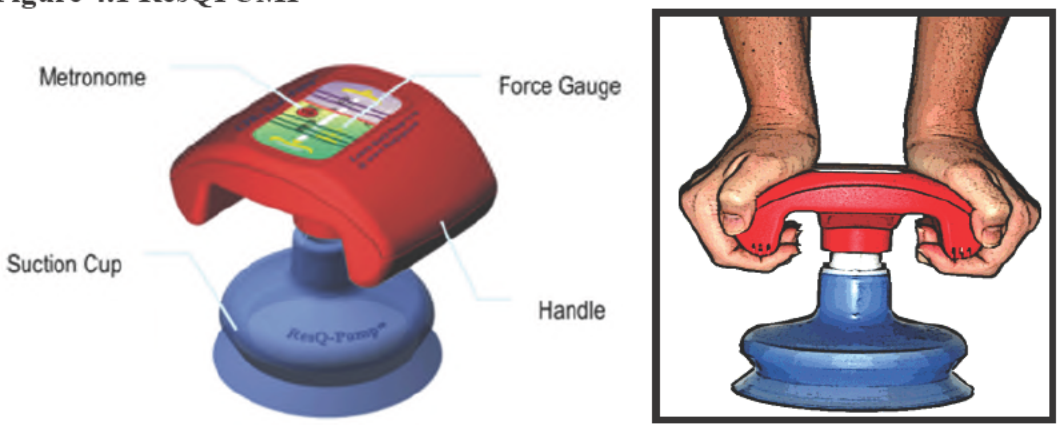
The proposed indications for use for the ResQCPR System are:

> The ResQCPR System is intended for use in the performance of CPR to increase survival with favorable neurologic function in patients with non-traumatic cardiac arrest.

4.2 Device Overview

The ResQCPR System is a manual CPR system that consists of two components: the ResQPUMP ACD-CPR device and the ResQPOD ITD 16 impedance threshold device. The individual ResQCPR System components are referred to as ACD-CPR device, or ResQPUMP, and impedance threshold device (ITD), or ResQPOD; their combined use is referred to as ResQCPR. The ResQPUMP is used instead of a pair of hands during the performance of CPR (**Figure 4.1**). It is a hand-held device that attaches with a suction cup to the skin over the mid-sternum and assists the rescuer in: 1) compressing the chest during CPR and 2) actively lifting upward during the decompression phase of CPR. The ResQPUMP has a force gauge to provide user feedback regarding the depth of compression and force needed for active decompression. It also has an audible metronome that beeps 80 times/minute to provide the rescuer with the correct compression rate.

Figure 4.1 ResQPUMP



The ResQPOD is a valve system that impedes respiratory gases from entering into the patient's thorax when pressures within the thorax are <0 atmospheres but allows for positive pressure ventilation with minimal resistance (<5 cm H_2O) and for expiration of respiratory gases with minimal resistance (<5 cm H_2O) (**Figure 4.2**). The ResQPOD has a secondary valve system with a resistance of -16 cm H_2O that opens when the pressure inside the thorax is <-16 cm H_2O, which may occur if the patient begins to breathe spontaneously. The ResQPOD is designed to fit on a face mask or advanced airway device and should be removed when CPR is not being performed. The ResQPOD also has timing lights that flash at a rate of 10 per minute, thereby providing the rescuer with the correct ventilation rate.

Figure 4.2 ResQPOD ITD 16

ACD-CPR transforms the human chest into an active bellows but does not, in itself, significantly impact the airway pressures during CPR. The ITD acts to lower intrathoracic pressure by impeding the inflow of respiratory gases during the decompression phase of CPR. Preclinical hemodynamic studies have shown that the synergistic effects of the combined devices result in enhanced venous return to the heart and lower intracranial pressure, and thus an increase in cardiac output and blood flow to the heart and brain during CPR. In addition to the hemodynamic benefits, the ResQCPR combination also provides rescuers with auditory and visual cues to assist in the correct performance of CPR.

4.3 System Components

ResQPUMP ACD-CPR Device

The ResQPUMP ACD-CPR device is shown in **Figure 4.1**. It is a reusable device that includes a handle to ensure a firm grip, a force gauge with a visual display of the forces exerted during chest compression and decompression to provide feedback, and a metronome to guide compression/decompression rate. As shown in **Figure 4.3**, the ACD-CPR device is operated manually. It is placed on the patient's chest and the handles are gripped by the operator as shown. The force gauge has visual targets based on chest compliance, with 65 lbs of pressure for subjects with softer compliance, 65-90 lbs for subjects with average compliance, and 110 lbs for subjects with stiffer compliance. Rescuers are instructed to use the gauge as follows: 1) compress the chest 2 inches as per AHA guidelines, 2) observe the force required on the gauge, 3) use that force as a guide, and 4) pull up after each compression until just before suction is lost or to about -15 lbs. The handle also includes a battery-powered audible metronome to assist in proper timing (duty cycle) of chest compressions (80 compressions per minute). After each compression, the rescuer pulls the ACD-CPR device upward, actively re-expanding the chest to

its natural resting position (fully recoiled) (**Figure 4.4**). The upward force is applied at the same time the chest naturally recoils after each compression. Active decompression assures that the chest fully recoils back to its resting position after each compression. This effort is intended to also correct the problem of leaning on the chest or incomplete chest decompression.[32] Full recoil increases the negative intrathoracic pressure and helps to create a greater vacuum within the thorax.

Figure 4.3 Operation of the ResQPUMP

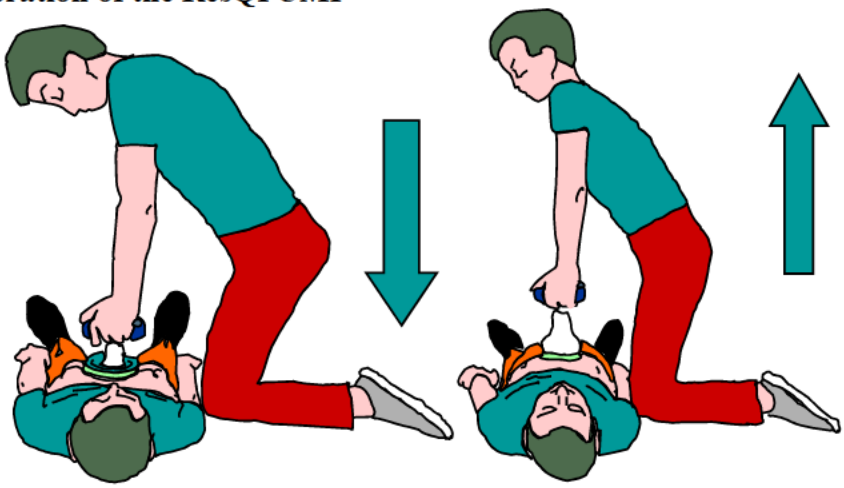
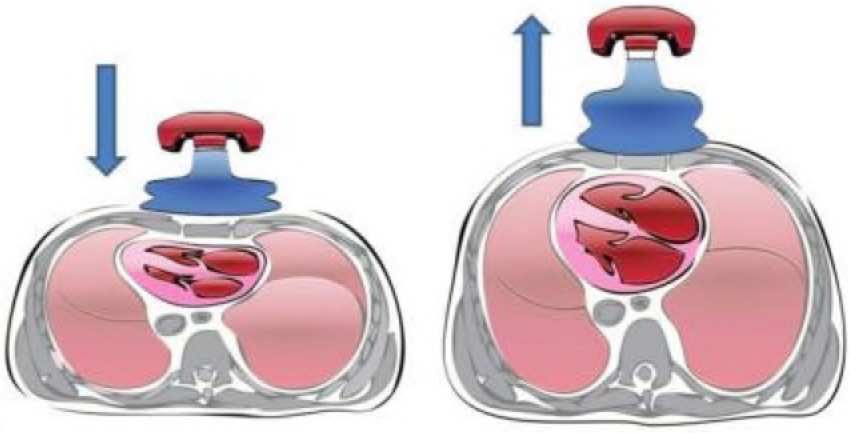


Figure 4.4 Effect of ResQPUMP during Compression and Decompression

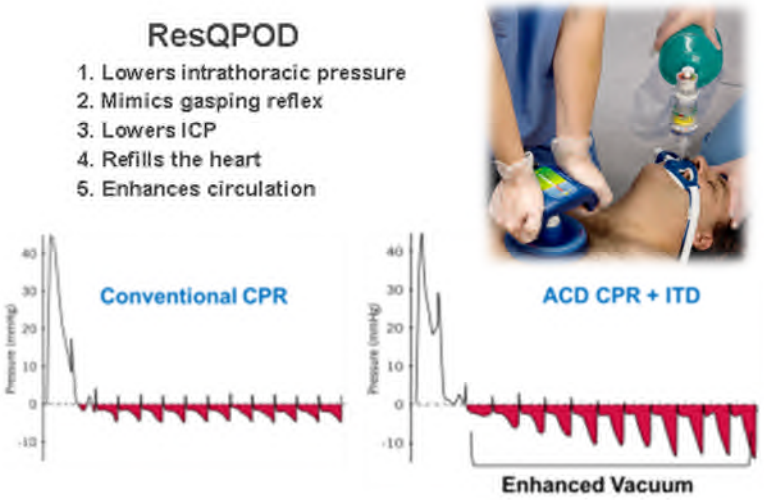


ResQPOD ITD 16 Impedance Threshold Device

The ResQPOD ITD 16 (**Figure 4.2**) is a single-use disposable valve system that limits passive air entry into the lungs during chest compressions, thereby reducing intrathoracic pressure. The ITD device is inserted in the airway circuit between the patient and the ventilation source and is designed for connection to either a face mask (with or without an oral or nasal airway) or advanced airway. It does not restrict the patient's ability to exhale, nor the rescuer's ability to ventilate. During CPR, the ResQPOD lowers intrathoracic pressure during the decompression phase of CPR. Each time the chest recoils after a compression, a small silicone diaphragm within the ResQPOD closes, thereby preventing respiratory gases from rushing into the lungs as a result

of the recoil vacuum. This secondarily causes a reduction in intrathoracic pressures to below 0 atmospheres of pressure during the chest recoil phase, as shown in **Figure 4.5**. The reduction in intrathoracic pressure during the recoil phase of CPR, highlighted by the shaded areas in this figure, serves to enhance the refilling after each compression.

Figure 4.5 Effect of the ResQPOD ITD 16 during Compression and Decompression



As described more fully below, intracranial pressure (ICP) is also reduced during the decompression phase with the ResQPOD. These physiological mechanisms mimic the gasping response described above in **Section 3.2** that similarly creates a reduction in intrathoracic pressure. Respiratory gases pass through the ResQPOD in a unique manner during each phase of CPR. With chest compressions, respiratory gases exit the thorax with minimal resistance (< 5 cm H_2O). With positive pressure ventilation, respiratory gases are delivered to the lungs with minimal resistance (< 5cm H_2O). During chest wall decompression, the ResQPOD impedes respiratory gases from entering the thorax unless the pressure in the thorax exceeds -16 cm H_2O (e.g., if the patient starts to breathe spontaneously,), in which case a secondary safety valve within the ResQPOD opens. Importantly, in the instructions for use, rescuers are directed to remove the ResQPOD when not performing CPR so if the patient starts to breathe on their own after a successful resuscitation effort there is no resistance to spontaneous inspiration.

4.4 Principles of Operation

The ResQPUMP and ResQPOD work synergistically to optimize blood flow to the heart and brain during ResQCPR. The ResQPUMP functions during the compression phase to compress the chest 2 inches in a manner analogous to a pair of hands during S-CPR. During the active decompression phase, the thorax is rapidly expanded, thereby transforming the chest into an active bellows. When ResQPUMP is used in combination with the ResQPOD, the active chest wall decompression results in a greater negative intrathoracic pressure since the ResQPOD transiently blocks respiratory gases from entering the lungs (**Figure 4.6**). Functionally, the greater negative intrathoracic pressure creates a more negative pressure inside the thorax. This, in turn, enhances venous flow back to the right heart in a manner analogous to a clinical Mueller maneuver (inspiration against a closed glottis).[33] As a consequence, the heart is refilled more

effectively after each compression when blood is propelled out of the heart. In addition, the greater intrathoracic vacuum results in a reduction in intracranial pressure, which in turn enhances forward blood flow.[8]

Figure 4.6 Creation of Negative Intrathoracic Vacuum

4.5 Summary

The ResQCPR System is designed to non-invasively optimize circulation of blood to the heart and brain during CPR. While each component by itself can enhance circulation during CPR, the combination works best synergistically to compress and expand the chest with each compression-decompression cycle and to harness the decompression phase vacuum to draw more venous blood back to the heart from the brain and other non-thoracic venous compartments of the body. This, in turn, helps to refill the heart after each compression and to reduce resistance to forward cerebral blood flow. In addition to achieving the desired physiologic effect of enhancing vital organ circulation, each of the device components has additional features to help rescue personnel perform CPR correctly.

5 PRECLINICAL DATA

5.1 Overview

Nonclinical studies were performed beginning in 1995 as part of continued research efforts to elucidate the physiologic mechanisms of action and preclinical benefits of using prototypes of the ResQPOD ITD 16 in animal models of cardiac arrest.[4,7,8,21,34-65] These studies focused on ways to enhance blood pressure, perfusion of the heart and brain, and survival rates with the ITD in combination with S-CPR and ACD-CPR. These studies have elucidated the mechanisms of action of S-CPR+ITD and ResQCPR. Detailed information regarding the preclinical studies summarized here were included in the PMA for the ResQCPR System.

The animal studies consistently demonstrated that when an ITD was used during either S-CPR or ACD-CPR airway pressure and intrathoracic pressure were lower (i.e., more negative) during the chest recoil phase. In these studies, airway pressures measured in the trachea were often used as a surrogate for intrathoracic pressure. The enhanced negative intrathoracic pressure generated with the ITD was consistently observed to be the driving force that pulled more blood back to the heart and this process in turn refilled the heart after each compression more effectively. In addition, the ITD-enhanced decrease in airway pressure during the recoil phase of CPR was transmitted to the brain with a resultant decrease in intracranial pressure (ICP) during the decompression phase of CPR. This lowered resistance to forward flow and thereby augmented brain flow by a second mechanism as well.[21,61,62]

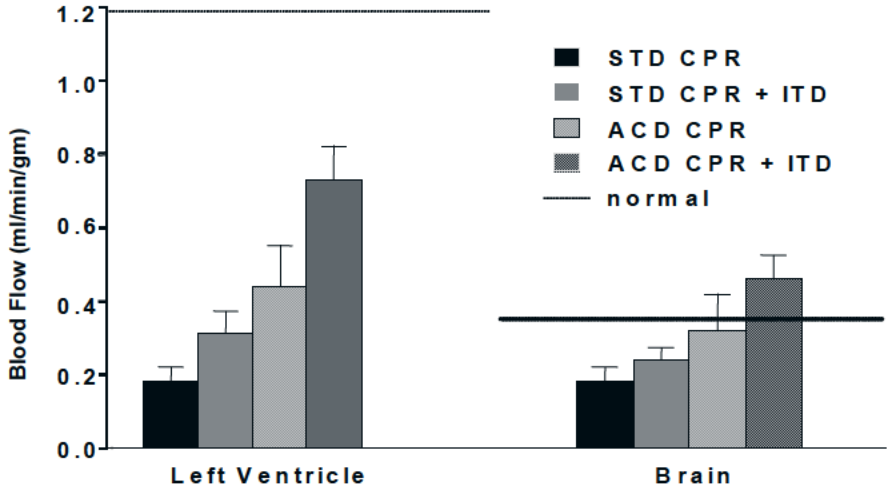
A number of different animal studies performed by the Company as well as by independent investigators have demonstrated the physiological benefit of use of an ITD with S-CPR and with ACD-CPR, in terms of improved hemodynamics, perfusion, and survivability with good neurological function 24 hours after cardiac arrest.[4,7,35,38,60,63,64] These studies were performed with ITDs that functioned in an analogous manner to the ResQPOD ITD 16. The relevant studies that demonstrate the physiological impact of the ITD on heart and brain circulation are described below.

Overall, the preclinical studies demonstrated a consistent augmentation of blood perfusion to the heart and brain during CPR with the prototypes of the ResQCPR System. There were no safety issues observed with this approach when compared with S-CPR alone or ACD-CPR alone.

5.2 Increased Blood Flow to the Heart and Brain

One study in 17 pigs compared blood flow to the heart and brain with ACD-CPR alone versus ResQCPR System prototypes.[7] During CPR with ResQCPR System prototypes blood flow to the brain was normal whereas with ACD-CPR alone it was significantly less. Blood flow to the heart was ~70% of normal with ResQCPR System prototypes versus <50% with ACD-CPR alone. A second study compared the same parameters with S-CPR alone versus S-CPR +ITD alone.[4,65] The results from those two studies are shown in **Figure 5.1**.

Figure 5.1 Effect of an ITD on Heart and Brain Blood Flow during CPR

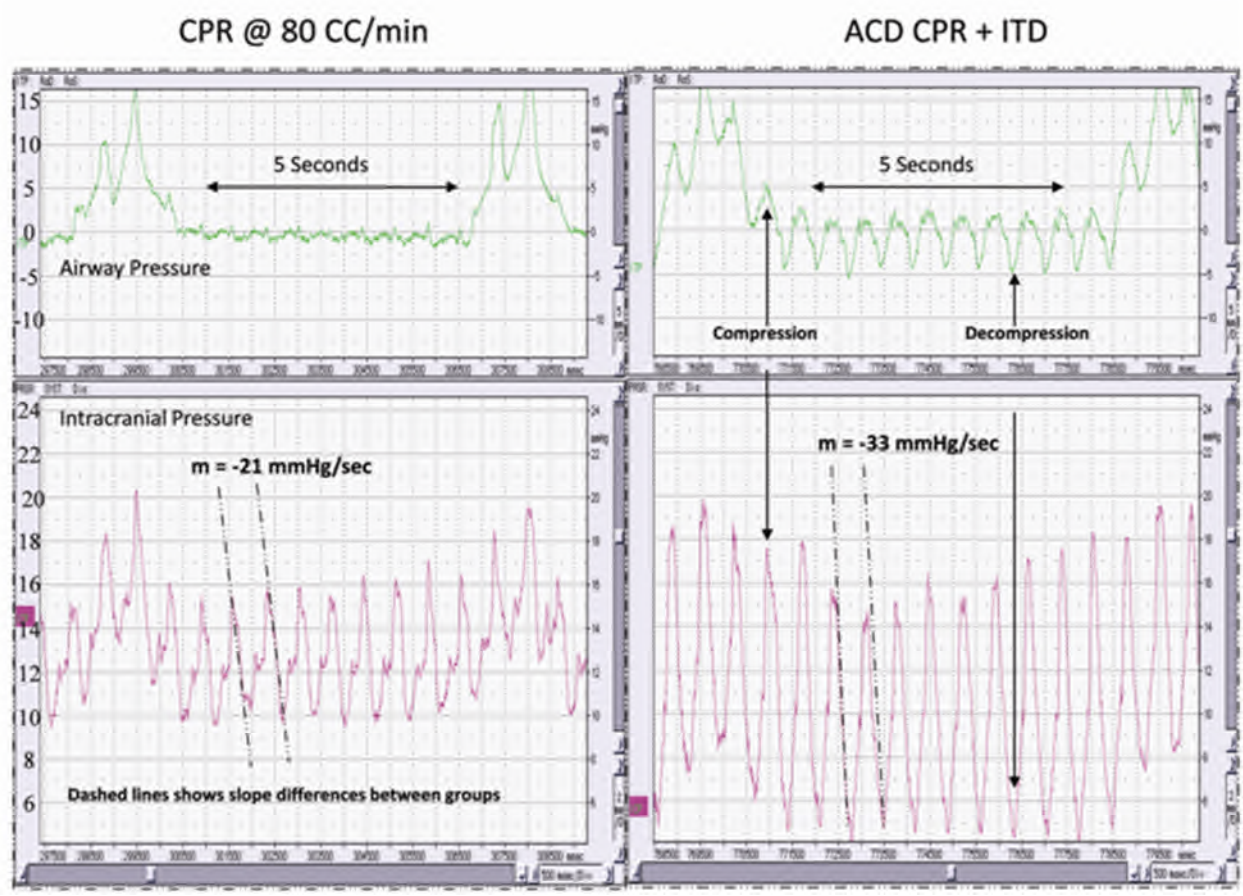


In **Figure 5.1**, data shown labeled ACD CPR + ITD was generated with ResQCPR System prototypes. Coronary perfusion pressures and end tidal CO_2 values have also been shown to be significantly higher with ResQCPR System prototypes versus ACD-CPR alone.[38]

5.3 Effect of ResQCPR on Intracranial Pressure and Survival with Favorable Neurological Function

Metzger et al. compared the effects of S-CPR alone versus the ResQCPR using ResQCPR System prototypes on intracranial pressure (ICP), cerebral perfusion pressure, and 24 hour survival in 26 pigs.[8] Compression and decompression force gauges were used to monitor the forces applied during CPR. In 9 pigs changes in airway pressure and intracranial pressure were recorded simultaneously during S-CPR (left) and during ResQCPR (right) as shown in **Figure 5.2**. The ResQCPR prototypes lowered airway pressures, a surrogate for intrathoracic pressures, and ICP more rapidly and to an absolute lower value during the decompression phase of ResQCPR when compared with S-CPR alone. The greater reduction in ICP generated with the ResQCPR resulted in enhanced cerebral circulation. Calculated cerebral perfusion pressure (in mmHg) (mean ± SEM) values were 21.9 ± 1.2 with the ResQCPR prototypes vs. 8.9 ± 0.8 with S-CPR, $p < .0001$). After 8.5 minutes of untreated ventricular fibrillation and 6 minutes of CPR, 24 hour survival rates with favorable neurological function were significantly higher in the ResQCPR-treated pigs (88%, 7/8) versus S-CPR alone controls (22%, 2/9).[8]

Figure 5.2 Mechanisms of Benefit and Lowering ICP



5.4 Summary

Multiple studies in porcine models of cardiac arrest have demonstrated that circulation to the heart and brain was consistently higher with ResQCPR prototypes versus S-CPR. No study showed any harm from the device combination or a worse effect with ResQCPR System prototypes versus controls. In these studies, blood flow to the heart and brain during S-CPR was observed to be approximately 20-30% of normal. By contrast, during CPR performed with ResQCPR System prototypes blood flow to the heart was approximately 70% of normal and blood flow to the brain was restored to normal values.[7,8,38,59,60] These studies demonstrated that the mechanism of action of the ResQCPR System involves harnessing the body's thoracic pump to circulate blood to the heart and brain more effectively than S-CPR. This, in turn, resulted in a consistently higher likelihood for successful resuscitation and neurological awakening.

6 DEVELOPMENTAL CLINICAL STUDIES

At present, the ResQPUMP is not available in the United States. A device called the CardioPump, which is structurally and functionally identical to the ResQPUMP, is sold outside the U.S. as an alternative to manual CPR for use in patients in cardiac arrest. As described previously in **Section 3.3**, the ResQPOD 10 is sold in the U.S. and the ResQPOD 16 is sold outside of the U.S.

6.1 Overview

Over the past 25 years, there have been multiple clinical studies evaluating ACD-CPR alone, S-CPR+ITD and ResQCPR. These studies are discussed in this section.

6.2 Prior Studies on ACD-CPR Alone

There have been several studies comparing ACD-CPR alone versus S-CPR alone for the treatment of OHCA. These studies include hemodynamic studies and clinical trials. Some of the studies demonstrated no clinical benefit of the ACD-CPR device studied and others have reported a significant benefit in terms of survival, up to one year. [66-79] A summary Table of representative published clinical ACD-CPR papers showing the primary study endpoints is found in **Section 11, Appendix 1**.

One study relevant to this current PMA application was performed at the University of Minnesota in 1994, by Shultz et al.[60] It was during the performance of this study that the concept of an inspiratory impedance threshold device (ITD) was discovered. In that study, 21 patients undergoing placement of implantable cardioverter defibrillators (ICDs) were randomized to receive either S-CPR or ACD-CPR alone with a ResQPUMP prototype for brief periods of time if and when their newly implanted ICDs failed to defibrillate after induction of ventricular fibrillation. Mean minute ventilation was significantly higher with the ResQCPR prototype alone, 168.4±68.6 mL, compared with S-CPR, 97.3±65.6 mL ($n=7$, $p<.001$), supportive of the concept that active decompression during CPR transformed the thorax from a passive to an active bellows. However, intrathoracic pressures were similar during the decompression phase of both S-CPR and ResQPUMP CPR. In an effort to understand this observation, one of the investigators blocked the endotracheal tube with his thumb during the chest decompression phase. With an occluded endotracheal tube during the active decompression phase of CPR using the ResQPUMP prototype, intrathoracic pressures were markedly lower (-11.4±6.3 mm Hg) compared with an open endotracheal tube during S-CPR (-0.8±4.8 mmHg) ($n=6$, $p<0.04$). These findings provided the first indication that transient occlusion of the airway during the decompression phase of ACD-CPR would enhance negative intrathoracic pressure, which could result in greater venous return to the heart, similar to a clinical Mueller maneuver. This study contributed to the invention of the ResQPOD ITD and the subsequent studies on the ITD alone and in combination with ACD-CPR.

6.2.1 Conclusions from Clinical Studies of ACD-CPR Device Alone

Prior clinical studies have suggested a benefit of ACD-CPR compared with S-CPR, but there are insufficient data indicating that this method by itself is superior to S-CPR in terms of survival. Of note, no studies to-date demonstrated a decrease in survival from ACD-CPR when compared with S-CPR.

Building upon the study from Shultz et al. [60] at the University of Minnesota, the ResQPOD has become a critical component of the ResQCPR System. Without the ResQPOD, respiratory gases are drawn immediately into the lungs with active decompression, which significantly reduces the augmentation of negative intrathoracic pressure during the chest recoil phase, thereby minimizing the potential value of the ResQPUMP. In 2005, Advanced Circulatory Systems licensed the rights to the ACD-CPR patent from the University of California in order to combine ACD-CPR with the ITD in the current ResQCPR System. Therefore the ResQPUMP should be used in conjunction with the ResQPOD for maximum effectiveness, as demonstrated in the pivotal ResQTrial (**48** and **8**).

6.3 Prior S-CPR +ITD Clinical Trials

The first double-blind, randomized studies with a ResQPOD prototype by Pirrallo and Aufderheide demonstrated that hemodynamic parameters were improved with S-CPR+ the ResQPOD prototype by itself, but the quality of CPR was difficult to control and maintain.[80] Those studies showed that systolic blood pressures were doubled when an active ResQPOD prototype was used in subjects with an OHCA. They also demonstrated that subjects were commonly excessively ventilated and that rescuers frequently leaned on the chest and did not allow the chest to fully recoil during S-CPR. These two observations were subsequently shown to be harmful in a porcine model of cardiac arrest, reduced the effectiveness of the ResQPOD prototype. [81-84] These findings contributed to the addition of ventilation timing lights that are part of the ResQPOD ITD 16. In subsequent clinical studies with S-CPR the ResQPOD was found to be most effective when incorporated in a systems-based approach where significant attention was paid to the quality of S-CPR.[21], [85]

Table 6.1 provides a summary of 11 clinical trials where S-CPR+ITD was employed. [21,80,84-92] The primary study endpoint results are shown. Some of the studies were performed with a prototype ResQPOD without the ventilation timing light.[80,84] As shown in this table, 10 of 11 studies were positive and one, the ROC PRIMED trial, was neutral. The positive studies demonstrated improved hemodynamics and an increase in survival rates with the active ResQPOD. [21,80,84-92] The 2010 American Heart Association (AHA) Guidelines provided the following recommendation: "The use of the ITD may be considered by trained personnel as a CPR adjunct in adult cardiac arrest (Class IIb)."[93]

Table 6.1 Clinical Trials with Standard CPR (S-CPR) and the Impedance Threshold Device (ITD)

Journal Citation	CPR Method	Trial Design	S-CPR (Control) No. of patients	S-CPR+ITD No. of patients	Endpoint	Results	p-value; Odds Ratio (95% CI)
[80]Pirrallo et al. Resuscitation 2005;66:13-20	S-CPR ± ITD (sham vs active)	Prospective, double blind, randomized; prehospital	12	10	Systolic blood pressure	Sham: 43 ± 15 mmHg Active: 85 ± 29 mmHg	p = 0.001
[84]Aufderheide et al. Crit Care Med 2005;33:734-740	S-CPR ± ITD (sham vs active)	Prospective, double blind, randomized; prehospital	116	114	1°: Survival to ICU admission – all pts	Sham: 17.2% Active: 25.4%	p = 0.13; 1.64 (0.87, 3.10)
[86]Thayne et al. Resuscitation 20 05;67:103-108	S-CPR ± ITD	Prospective vs historical control; prehospital	808	181	1°: Alive upon ED admission – all pts	No ITD: 22% With ITD: 34%	p = 0.005
[21]Aufderheide et al. Crit Care Med 2008;36:S397-S404	S-CPR ± ITD	Prospective vs historical control; prehospital	1750	920	1°: Survival to hosp discharge – all pts	No ITD: 9.3% With ITD: 13.6%	p = 0.0008; 1.541 (1.192, 1.990)
[88]Hinchey et al. Ann Emerg Med 2010; 56:348-357	S-CPR ± ITD	Prospective, 3-phase, systems-based approach vs historical control; prehospital	794	571	Survival to hosp discharge – all pts	No ITD: 7.3% With ITD: 11.5% Absolute increase from baseline to 3rd phase: 4.2 to 11.5%	95% CI for absolute increase of 7.3% from baseline (3.7, 10.9)
[89]Thigpen et al. J Resp Care 2010; 2010; 55(8):1014-1019	S-CPR ± ITD	Prospective, systems-based approach vs historical control; inhospital	246	261	1°: Survival to hosp discharge – all pts	No ITD: 17.5% With ITD: 28%	p = 0.006; 1.83 (1.17, 2.88)
[87]Aufderheide et al. Heart Rhythm 2010; 7: 1357-1362	S-CPR ± ITD	Prospective, systems-based approach vs historical control; prehospital	1641	1605	1°: Survival to hosp discharge – all pts	No ITD: 10.1% With ITD: 13.1%	p = 0.007; 1.34 (1.08, 1.68)

Journal Citation	CPR Method	Trial Design	S-CPR (Control) No. of patients	S-CPR+ITD No. of patients	Endpoint	Results	p-value; Odds Ratio (95% CI)
[85]Lick et al. Crit Care Med 2010; 39: 26-33	S-CPR ± ITD	Prospective, systems-based approach vs historical control; prehospital	107	247	1°: Survival to hosp discharge – all pts	No ITD: 8.4% With ITD: 19%	p = 0.011; 2.56 (1.17, 6.17)
[94]Aufderheide et al. ROC Trial NEJM 2011; 365:9:798-806	S-CPR ± ITD (sham vs active)	Prospective, double blind, randomized, cross-over; prehospital	4345	4373	Survival to hospital discharge with good neurologic function	Sham ITD: 6.0% Active ITD: 5.8%	p = 0.61

The NIH Resuscitation Outcomes Consortium (ROC) PRIMED study was the largest of these clinical trials. It was a double-blinded randomized controlled trial that compared an active versus sham ITD and 30 seconds versus 3 minutes of CPR followed by analysis and shock for ventricular fibrillation. The active ITD in the study was identical to the ResQPOD 16 used in the ResQTrial except that it was opaque for the purposes of blinding. The study was performed in 10 North American cities, and was designed using a factorial study design. At the time the study was terminated there was no observed benefit or harm in terms of survival to hospital discharge with a mRS ≤3 in subjects with an OHCA of presumed cardiac etiology (S-CPR + sham ResQPOD (260/4345 or 6%) versus S-CPR + an active ResQPOD (254/4373 or 5.8%). More recently, Idris et al. demonstrated that there was a wide range of chest compressions during the ROC PRIMED study which was unknown to the investigators when the primary results were published.[94] Idris showed that chest compression rates ranged from <50 to over 250 per minute.[19] Stiell et al. also recently performed a post-hoc analysis that examined the quality of chest compressions in the ROC PRIMED study.[95] Similar to compression rate, these authors reported that the compression depth varied widely and was often inadequate.[96] Using a validated ROC PRIMED database made available by the NIH, the Company performed exploratory analyses similar to those of Idris and Stiell to examine the relationship between compression rate and depth and outcomes with a sham versus active ResQPOD.

These analyses with data from the ROC PRIMED database demonstrated that when S-CPR was performed according to the 2005 AHA Guidelines for compression rate and depth, the Guidelines in place when the study was performed, use of the active ResQPOD resulted in more subjects who were discharged alive with favorable neurological function compared with the sham ResQPOD. If CPR rates were not in accordance with the Guidelines, there was no difference in outcomes between the sham and active ResQPOD. Therefore, it appears that the quality of the CPR delivered had a significant effect on the study outcomes.

Conclusions from Clinical Studies of S-CPR+ the ResQPOD alone

Ten of the eleven clinical studies that assessed the use of S-CPR together with the ResQPOD or a ResQPOD prototype reported a statistically significant clinical benefit. A post-hoc analysis of the only neutral study, the ROC PRIMED study, demonstrated a clinical benefit with the ResQPOD when high quality S-CPR was performed according to the AHA Guidelines. None of the 11 studies reported safety concerns with use of the ResQPOD.

6.4 Prior Clinical Trials with ResQCPR System Prototypes

In addition to the ResQTrial, four prior European clinical studies evaluated the hemodynamic effects, safety and clinical effectiveness of ResQCPR using functional prototypes of the ResQCPR System. The results showing the primary study endpoints are summarized in **Table 6.2**. The study devices used in the four European clinical trials were a CardioPump, manufactured by Ambu, Internationale for the performance of ACD-CPR and a prototypic ITD, manufactured by Advanced Circulatory Systems Inc. The Ambu CardioPump was different in design compared with the ResQPUMP that is part of the ResQCPR System and used in the ResQTrial, but it functioned in the same manner. The CardioPump had a circular-shaped handle (in contrast to the ResQPUMP's rectangular ergonomically-designed handle) and it lacked the cushion element of the ResQPUMP that contacts the patient's chest. During the European

studies, ResQCPR was performed at either a rate of 90 or 100 compressions/minute. The prototype ITDs studied in the four European trials were different from the ResQPOD used in the ResQTrial in that they did not include the timing lights for guiding ventilations during CPR. In addition, the safety check valves had a resistance of -21 cm H_2O. Nonetheless, they functioned to augment negative intrathoracic pressure during ACD-CPR in the same manner as the ResQPOD used in the ResQTrial.

Table 6.2 Clinical Studies of Active Compression Decompression (ACD) CPR and the Impedance Threshold Device (ITD)[1]

Journal Citation	CPR Method	Design	Control Group (n)	Treated w/ Active ITD (n)	Endpoints	Results	p-value; Odds Ratio (95% CI)
[97]Plaisance et al. Circulation 2000;101:989-994	ACD ± ITD (sham vs active)	Prospective, single center, blinded, randomized; pre-hospital	10	11	systolic arterial pressure (mean peak) diastolic arterial pressure (mean peak)	Sham: 90 ± 6.4 mmHg Active: 108 ± 3.1 mmHg Sham: 36.5 ± 1.5 mmHg Active: 56.4 ± 1.7 mmHg	$p < 0.05$ $p < 0.001$
[98]Wolcke et al. Circulation 2003;108:2201-2205	S-CPR vs ACD +ITD	Prospective, single-center randomized; pre-hospital	107	103	Survival to 1 hour after witnessed arrest – all pts	S-CPR: 32% ACD+ITD: 51%	p = 0.006; 2.4 (1.28, 4.62)
[99]Plaisance et al. Resuscitation 2004;61:265-271	ACD ± ITD (sham vs active)	Prospective, multicenter, blinded, randomized; pre-hospital	200	200	Survival to 24 hours – all pts	Sham: 22% Active: 32%	p = 0.02; 1.67 (1.07, 2.60)
[100]Plaisance et al. Crit Care Med 2005;33:990-994	ACD ± ITD (sham vs active)	Prospective, Single-center, blinded, randomized; pre-hospital	13	13	Mean peak negative intrathoracic pressure during decompression with facemask 1°: Mean peak negative intrathoracic pressure during decompression with ET tube	Sham: -1.0 ± 0.73 mmHg Active: -4.6 ± 3.7 mmHg Sham: -1.3 ± 1.3 mmHg Active: -7.3 ± 4.5 mmHg	p = 0.003 p = 0.0009

These four European clinical studies demonstrated that use of ResQCPR prototypes resulted in improved hemodynamics, lower intrathoracic pressures during the chest decompression phase, increased circulation as measured by end tidal CO_2, and increased 1 and 24-hour survival rates. The physiologic and clinical outcomes in these studies are consistent with the findings in the pivotal ResQTrial. There were no safety concerns raised by these four clinical studies that included a total of 644 patients. Taken together, these four European studies provide evidence of a favorable risk/benefit profile, and support for the overall safety and efficacy of use of the ResQCPR System for treatment of patients with cardiac arrest.

6.5 Conclusions

Clinical studies with the two ResQCPR System components demonstrated a clinical improvement in hemodynamics and short-term survival rates. While studies of each component showed improvement, studies of the combination showed a consistent synergistic effect of even greater improvement in clinically meaningful outcomes. No safety concerns were raised by the four prior clinical trials related to either of the ResQCPR System components. All four clinical trials with prototypes of the ResQCPR System demonstrated a consistent and clinically important hemodynamic and short-term survival benefit of the device combination versus controls. These positive findings provided a sound scientific rationale for performing the pivotal ResQTrial in the U.S.

7 ResQTrial PROTOCOL SUMMARY

7.1 Overview

The ResQTrial was a prospective, multicenter, two-arm, randomized, controlled, partially-masked, NIH-funded clinical trial designed to compare the current standard of care for patients in cardiac arrest (manual closed-chest standard CPR [S-CPR]) *versus* the combination of active compression decompression (ACD) plus an impedance threshold device (ITD) in subjects with an out-of-hospital cardiac arrest of presumed cardiac etiology (the ResQCPR System). Subjects with non-traumatic out-of-hospital cardiac arrest (OHCA) were randomized to receive S-CPR (the control group) or ResQCPR (the intervention group). The primary analysis included those patients in the intention-to-treat (ITT) population who were determined to have a cardiac arrest due to cardiac cause and met all other final inclusion criteria (the modified (m) ITT population). The primary effectiveness endpoint was the composite endpoint of survival to hospital discharge with favorable neurological function in the mITT population. Enrollment in the pivotal phase took place from March 2006 to July 2009, and one-year follow-up was completed for all subjects in July 2010.

The ResQTrial was conducted in accordance with the Company's clinical operating procedures, which were developed based upon accepted best clinical practice guidelines (ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1). Due to the nature of out-of-hospital resuscitation research and the study population, there were a number of study design and conduct challenges. The Company anticipated these challenges and implemented quality control measures to address them, as described in the sections below.

7.2 Study Design and Objective

The ResQTrial was a prospective, multicenter, two-arm, randomized, controlled, partially-masked, NIH-funded clinical trial designed to compare the current standard of care for patients in cardiac arrest, manual closed-chest standard CPR (S-CPR) versus the combination of active compression decompression (ACD) plus an impedance threshold device (ITD) in subjects with an out-of-hospital cardiac arrest of presumed cardiac etiology. The study was designed to test the hypothesis that treatment with ResQCPR increases survival to hospital discharge with favorable neurologic function versus S-CPR in subjects with OHCA of cardiac etiology.

7.3 Study Population

The study was conducted in seven distinct geographic locations in the US: Minneapolis, MN; St. Paul, MN; Whatcom County, WA; Oshkosh, WI; Oakland and Macomb Counties, MI; Washtenaw and Livingston Counties, MI; and Indianapolis, IN. These sites included 46 EMS agencies in urban, suburban and rural areas, encompassing a total population of ~2.3 million. A total of 40 hospitals participated in the care of the subjects in this trial. The "screening population" for the study is defined as all subjects with presumed cardiac arrest occurring within the primary response area of the participating EMS systems.

Prior to beginning enrollment in the pivotal study, a run-in phase was required at all study sites in order to confirm that the site was able to successfully execute all aspects of the study protocol. The run-in phase was performed to assure that the sites were able to implement the study protocol effectively before initiation of the pivotal phase and to provide investigators with an indication of the relative differences between study groups, even though the investigators and the Company were blinded to aggregate results. During the run-in phase, subjects were randomized and entered into the study according to the study protocol. Subjects (or their representatives) were also notified and/or consented per protocol. Adverse events and complications were monitored and reported to the Clinical Events Committee (CEC) per the Investigational Plan. Study monitors conducted an evaluation of the study site to assure that the objectives of the run-in phase had been successfully met, and the findings were documented in a site certification report. Upon site certification, the site was thus permitted to transition to the pivotal enrollment phase. Run-in phase outcome data were not to be combined with data from the pivotal phase when determining the primary study endpoint.

7.3.1 Study Enrollment Criteria

7.3.1.1 Inclusion Criteria

All adult subjects initially presumed or known to be 18 years of age or older who presented with presumed non-traumatic, out-of-hospital cardiac arrest (OHCA) and who were candidates for resuscitation attempts by EMS personnel were enrolled in the study and randomized to one of the two treatment groups.

7.3.1.2 Exclusion Criteria

All subjects initially presumed or known to be < 18 years of age who presented with:

1. obvious or likely traumatic injuries causing cardiac arrest,
2. pre-existing DNR orders,
3. signs of obvious clinical death or conditions that preclude use of CPR,
4. subjects experiencing in-hospital cardiac arrest,
5. those with a recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known), and
6. subjects whose family or legal guardians requested that the subject not be entered in the study at the time of arrest.

7.4 Study Treatment

Subjects were assigned to S-CPR (control treatment) or to ResQCPR (investigational treatment). S-CPR was initiated by the first arriving Basic Life Support (BLS) or Advanced Life Support (ALS) Emergency Medical Services (EMS) providers as soon as possible for subjects in both study groups. S-CPR, defibrillation, and ALS treatment were performed consistent with local policy and per the American Heart Association (AHA) guidelines for cardiopulmonary resuscitation.[101,102] Subjects received 2 minutes of CPR prior to analyzing the subject's cardiac rhythm. The compression:ventilation ratio was 30:2 during BLS for both CPR techniques. ResQCPR was initiated as soon as possible by first arriving BLS or ALS EMS providers and

delivered at a rate of 80 compressions per minute. A force gauge on the ResQPUMP was used to help achieve the recommended compression depth and complete chest recoil. For subjects randomized to the ResQCPR group, rescuers were instructed to initially attach the ResQPOD between the ventilation bag and facemask and then relocate it to the advanced airway, once established. The ResQPOD was removed if the subject had a return of spontaneous circulation (ROSC) and reapplied if re-arrest occurred.

The devices and facemask for the ResQCPR group, or a facemask alone for the S-CPR group, were packaged together in a study bag and carried by rescue personnel per a weekly randomization schedule. The same brand/style facemask was used for all subjects regardless of randomization arm (King Systems; Indianapolis, IN). CPR efforts in both groups were encouraged for at least 30 minutes on scene before terminating the resuscitation attempt. ResQCPR treatment, if ongoing, was stopped upon arrival to the hospital. All site investigators encouraged their in-hospital colleagues at the receiving hospitals to provide post-resuscitation care per the recommendations of the AHA Guidelines, including therapeutic hypothermia and coronary revascularization in all appropriate candidates, regardless of the method of CPR used in the field. However, no in-hospital care was specifically identified or recommended in the study protocol.

7.5 Consent Process

This is the first PMA application for a CPR device using a study conducted under 21 CFR §50.24, *Exception from Informed Consent under Emergency Circumstances* and related guidance. All aspects of the consent processes used during the study were shared with FDA as part of the IDE process. The entire protocol, including all portions focused on the process of exception from informed consent under emergency circumstances, was approved by the 26 participating local IRBs at the hospitals to which study subjects were likely to be transported. NIH, as the primary funding source of the study, approved the study protocol including the manner in which exception to informed consent was implemented. In addition, the NIH appointed a representative to the DSMB to provide further independent study oversight on this matter and study conduct in general.

The 21 CFR §50.24 regulation allows an IRB to authorize an investigation without prior informed consent for subjects in certain life-threatening situations where the investigation would be impossible without such a waiver. For the first time, these regulations provided the opportunity to evaluate new CPR devices but also presented some practical challenges.

Essential clinical study safeguards built into compliance with exception of informed consent include requirements for: 1) community consultation, 2) public notification, 3) establishment of an independent DSMB, and 4) subsequent public disclosure of study results. Investigators implemented a rigorous plan to meet these four requirements. This included meeting with hundreds of interested individuals in multiple public forums throughout the geographical area where the study would be conducted. At these meetings, the rationale for the study was presented and discussed and the study protocol was reviewed. Public notification that the study would be performed was provided in newspapers, radio, and television spots. All EMS agencies had to demonstrate they were in compliance with Federalwide Assurance for the Protection of Human

Subjects. In annual reports to the FDA and the NIH, the Company described in detail how each of these requirements was implemented at each study site. In addition, the Company and study sites were audited at different times by the FDA. No issues were raised by FDA or the NIH related to compliance by the Company or the sites with 21 CFR § 50.24 during the course of the study.

The subjects enrolled in this study were unconscious at the time of enrollment when CPR was initiated by EMS personnel. Informed consent for inclusion in the trial and continued participation was required from any subject, or their legally authorized representative, for all subjects who survived to hospital admission. Efforts to obtain consent were initiated as soon as the study personnel learned of a subject's admission to the hospital. A nurse or researcher trained to obtain consent during this difficult time initiated contact with the family or subject generally within the first two days. Due to the challenges of obtaining consent from family members or a subject who may be distraught given the clinical circumstances, the process of obtaining consent often extended over several days or weeks. All reasonable efforts were taken to obtain consent while also remaining sensitive to the emotional and psychological stress issues surrounding the acute medical crisis.

Informed consent was not required for subjects who died prior to hospital admission. For these subjects, the investigators sent a letter of notification to the family, as required by 21 CFR § 50.24, indicating that the subject was enrolled in the study. The letters were sent by certified mail which required a signature upon delivery so it was known that the letter reached the intended recipients. Notification could also have occurred by a phone contact that was documented.

Based on their interpretation of 21 CFR § 50.24 at the start of the ResQTrial, local IRBs would not allow investigators to gather data from the subjects' medical records in the absence of consent. In October 2008, nearly three years after the first subjects were enrolled in the ResQTrial, FDA issued a new guidance document (*Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials*) clarifying that companies could obtain data in emergency consent situations where informed consent was neither obtained nor denied.[10] In cases where the outcome data were not available due to the lack of a consent decision or a denial of consent, this new Guidance provided a regulatory means to review and include information from the subject's medical record up to the time consent was denied. If there was a lack of a consent decision or denial of consent occurred after the time of hospital discharge, then access to the subject's hospital discharge note in the medical record was, for the first time, available for review and inclusion in the ResQTrial based on this Guidance. The impact of the 2008 Guidance is summarized in **Table 7.1**.

Table 7.1 Impact of the 2008 FDA Guidance

Scenario	Pre 2008 Guidance	Post 2008 Guidance
Subject died prior to hospital admission	• All field data could be collected • Publicly available records, including public death records, could be used	• All field data could be collected • Publicly available records, including public death records, could be used
Subject admitted to hospital - Affirmative consent given	• All field data could be collected • Publicly available records, including public death records, could be used • All in-hospital medical record data could be collected	• All field data could be collected • Publicly available records, including public death records, could be used • All in-hospital medical record data could be collected
Subject admitted to hospital - Affirmative denial of consent	• All field data could be collected • Publicly available records, including public death records, could be used • In-hospital medical record data could not be collected	• All field data could be collected • Publicly available records, including public death records, could be used • Review of in-hospital medical record up to point of written consent denial
Subject admitted to hospital – neither affirmative consent nor denial	• All field data could be collected • Publicly available records, including public death records, could be used • In-hospital medical record data could not be collected	• All field data could be collected • Publicly available records, including public death records, could be used • Ability to petition local IRBs for subject information when consent was not obtainable

As a result, after the issuance of the 2008 guidance, the Company undertook an effort to obtain data in cases where outcome data were not available due to the lack of a consent decision or a denial of consent. The use of the revised Guidance by the Company was approved by 25 of the 26 IRBs and was described and reported to the FDA. The process of retrospectively reviewing and including cases in which the arrest occurred between 2005 and 2008 where the outcome data were not available due to the lack of a consent decision or a denial of consent began in early 2009. This resulted in the relatively late review of medical records for a number of subjects. This review consequently let to exclusion of some subjects from the mITT analysis population up to three years after their arrest in some cases. This process was conducted according to the Company's clinical operating procedures which included the standard data evaluation process, monitoring, and, when indicated, CEC review. As a result of the implementation of the 2008 FDA Guidance, investigators were able to obtain primary study outcomes on approximately 99% of all subjects enrolled in the study. Adherence to the 2008 FDA Guidance allowed for more complete data collection but, as an examination conducted at the end of the study revealed, did not alter conclusions related to the safety and relative effectiveness of the ResQCPR System as compared with S-CPR. **Section 8.9.7.5** provides the detail of this analysis. **Section 8.9.7.4** provides detail on the limited number of subjects for whom primary outcome data was unobtainable.

7.6 Randomization

Subjects were assigned to one of the two treatment arms on a 1:1 proportional basis using a prospective computer-generated block randomization weekly schedule prepared by an independent biostatistician. Sites posted the randomization schedule in fire stations and the schedule was available to the 911-dispatchers. To minimize randomization errors, study devices were to be physically removed from all EMS vehicles and placed in a locked location at the fire station during S-CPR randomization weeks. During ResQCPR weeks, the study devices were placed back in all EMS vehicles on a regular preset day and hour.

7.7 Blinding

Blinding could not be accomplished at the point of care due to the nature of the study and devices. However, individuals who performed the neurological assessments were blinded to the method of CPR used, as were individuals caring for the subjects in the hospital. The Company's Data Coordination Center (DCC) staff and study monitors were not blinded on an individual case basis, as these personnel were responsible for CRF data management, data query resolution, data entry into the study database, and other quality assurance activities.

All study personnel, however, both study site and Company personnel, as well as all members of the Clinical Events Committee (CEC), remained blinded to aggregate data based on treatment received until July 2010, after the final enrolled subject surviving to one year was assessed. More specifically, treatment groups were masked as Group A and Group B prior to unblinding with no indication as to the identity of the specific groups. The Company received copies of the DSMB reports that included masked Group A and Group B data and provided these reports to FDA and NIH on an annual basis. The DSMB requested to become unblinded to the identity of the specific groups in July 2009; this request to become unblinded was unknown to the Company and all other study personnel. An independent biostatistician was the only individual who was unblinded to aggregate study outcomes throughout the trial.

On September 5, 2012, FDA initiated a Bioresearch Monitoring ("BiMo") sponsor-monitor investigation at ACSI at the direction of the Review Branch. During the inspection, the FDA inspector determined that, if two separate reports generated for the DSMB were compared against one another, it was possible to unblind the study data by group.

The FDA inspector also contemporaneously described the company's reaction to this observation in the Establishment Inspection Report ("EIR"):

> "The company was very surprised to see this could be done with their reports; they acknowledged that yes it appears to be the case that you can unblind data, but adamantly disagreed that anyone did unblind data before dates allowed."

The FDA inspector interviewed the independent study biostatistician, the DSMB Chair, the NIH-appointed DSMB member, and the company's Chief Medical Officer, and reviewed company emails and correspondence related to the DSMB meetings. All company representatives and

independent study participants unequivocally denied unblinding during the study, other than when the DSMB appropriately chose to become unblinded in July 2009.

This inspection took place two years after the completion of the study and over one year after the PMA for the ResQCPR System was filed. During the entire course of the study, ACSI had been transparent with FDA and had submitted all DSMB reports on an annual basis to the Review Branch in CDRH/ODE, including the reports that contained all of the material questioned during the inspection.

The Company maintains that it has always been transparent with FDA and had submitted all DSMB study reports and quality assurance reports, as well as Annual Reports, to the Review Branch in CDRH/ODE on an annual basis during the study. Further, the Company maintains that it remained blinded to treatment-group specific aggregate data during the entire enrollment and follow-up phase of the study.

7.8 Study Endpoints

7.8.1 Primary Safety and Effectiveness Endpoint

The primary endpoint was survival to hospital discharge with favorable neurologic function, defined as a Modified Rankin Scale score (mRS) of ≤3 in the mITT population. This was a combined composite safety and effectiveness endpoint and was tested on a superiority basis versus S-CPR.

7.8.2 Secondary Safety Endpoint

The secondary safety endpoint was the overall rate of major adverse events through hospital discharge in the mITT population. Major adverse events to hospital discharge that contributed to the evaluation of this secondary safety endpoint included: death, cerebral bleeding/stroke, re-arrest, pulmonary edema, chest fractures, excessive bleeding and transfusion requirement, and internal thoracic and abdominal injuries. Other anticipated effects of CPR that were to be reported but not classified as major adverse events included vomiting during CPR and superficial skin bruising at the point of contact for chest compressions.

7.8.3 Secondary Effectiveness Endpoint

The evaluation of long-term neurologic function was assessed using the Cognitive Abilities Screening Instrument (CASI, Version E-1.1) at 90 days and 1 year post-cardiac arrest in surviving subjects.

7.8.4 Additional Pre-Specified Secondary Endpoints

Additional pre-specified secondary endpoints were:

1. Return of spontaneous circulation (ROSC), survival to hospital admissions and 24 hour, 30 day, 90 day and 1 year survival

2. Analyses based upon gender, age, witnessed status, CPR started <10 minutes from collapse versus >10 minutes, determined by the 911 call, study site, initial rhythm, cause of death (presumed cardiac versus non-cardiac), airway secured vs. unable to secure
3. Neurologic recovery assessed at hospital discharge, 30 days, 90 days and 1 year, using various neurologic assessment tools (Trail Making Tests (Part A and B), Beck Depression Inventory, Cerebral Performance Category, Overall Performance Category, Health Utility Index 3 (HUI3), Disability Rating Scale (DRS) and Mayo-Portland Adaptability Inventory (MPAI)
4. Quality of Life (QOL) at 1 year
5. Per protocol analysis based upon treatment delivered according to the randomization schedule
6. Run-in phase outcomes

7.9 Subject Assessments and Visit Schedule

Unlike many studies, there were no baseline visits with the subjects before they were enrolled based upon their need for CPR and their presentation in non-traumatic cardiac arrest. For those subjects who died in the field, all information related to the subject assessment was based upon the EMS run report and the call-in report to the research hotline as there was no hospital record for these subjects. For those who survived to hospital admission, the clinical study assessments, follow-up intervals, and visits performed are summarized in **Table 7.2**.

Table 7.2 Follow-Up Neurologic Assessments and Schedule

Endpoint and Follow-up Window	**Hospital Discharge** up to 5 days after discharge	**30-day Survival** within 30+/- 5 days	**90-day Survival** within 90 +/- 5 days	**1-year Survival** within 365 +/- 15 days
Modified Rankin Scale (mRS)	X (1° endpoint)			
Cerebral Performance Category (CPC)/ Overall Performance Category (OPC)	X	X	X	X
Health Utilities Index 3 (HUI3)	X	X	X	X
Disability Rating Scale (DRS)		X	X	X
Cognitive Abilities Screening Instrument (CASI)			X	X
Trail-Making Test (TMT)			X	X
Beck Depression Inventory II (BDI-II)			X	X
Mayo-Portland Adaptability Inventory-4 (MPAI-4)			X	
Quality of Life Survey (QOLS)				X

7.10 Statistical Methods Planned in the Protocol

7.10.1 Analysis of Primary Study Endpoint

Estimates of the composite endpoint of survival to hospital discharge with a favorable neurologic outcome were unavailable for the purposes of estimating the sample size when the protocol was written. Based upon historical control data from participating sites, it was assumed that survival to hospital discharge in the control arm, S-CPR, would be 6%, with a detectable improvement expected in the investigational ResQCPR treatment arm to 10.2% and an odds ratio of 1.77. As such, a total sample size of 1400 evaluable subjects was proposed for the study, with 700 subjects randomized to each of the two treatment arms to enable detection of clinical differences (odds-ratios) associated with a Type I error level of 0.049 and a statistical power of 80%, based on a continuity corrected Chi-Square test of equal proportions (i.e., odds-ratio equal to 1). A two-sided alpha of 0.022 was specified for the study before the the third study arm (S-CPR+ITD) was discontinued as described below in **Section 7.15.2**. In order to continue to maintain an overall error level of 0.049 after the discontinuation of the third study arm, the significance level was changed to 0.049 (Lan-DeMets group sequential alpha spending levels). The FDA approved this change to the Statistical Analysis Plan in early 2008.

7.10.2 Analysis Populations

ITT Analysis Population
A supplemental analysis was to be performed on all randomized subjects (ITT population) for whom data on study outcomes were available. The ITT population was defined as those subjects who met study enrollment criteria, as described in **Section 7.3.1,** above.

Primary (mITT) Analysis Population
The pre-specified inclusion criteria for the mITT analysis population were adult subjects who were initially presumed or known to be 18 years of age or older and presented with out-of-hospital cardiac arrest from presumed cardiac etiology and received CPR by EMS personnel for at least one minute. In addition, these had to be subjects whose airways were managed with a cuffed endotracheal tube, Combitube or laryngeal mask airway or facemask. The mITT analysis population was pre-specified as the primary analysis population for this study.

Pre-specified reasons for excluding patients from the primary analysis (mITT) population were:

1. were presumed or known to be < 18 years of age
2. had known or likely traumatic injuries causing cardiac arrest or cardiac arrest of presumed non-cardiac origin
3. had pre-existing DNR orders
4. had signs of obvious clinical death or conditions that preclude use of CPR
5. had a recent sternotomy with wound not appearing completely healed (if unknown) or less than six months (if known)
6. were intubated with a leaky or uncuffed advanced airway device or presence of stomas, tracheotomies or tracheostomies

7. had a complete airway obstruction that cannot be cleared or in whom attempts at advanced airway management are unsuccessful
8. had a family or legal representative request that the subject not be entered into the study
9. had an in-hospital cardiac arrest
10. who received less than one minute of CPR by EMS personnel
11. who re-arrested after hospital discharge and were already enrolled in the study after their index arrest

It is well established that subjects in cardiac arrest represent a heterogeneous population: some individuals are known to respond well to CPR. Others, about 35%, have a non-cardiac etiology and often respond poorly to CPR, regardless of the level of circulation provided, with little or no likelihood of survival with any treatment.[3,9,11] Therefore, analysis of the ResQTrial focused on subjects who have the capacity to benefit from CPR, the modified intention-to treat (mITT) population.

7.10.3 Sample Size Calculation and Interim Analysis

Sample sizes were estimated using the commercially available software package *nQuery Advisor* (Version 4, Statistical Solutions).

The study design assumptions were:

- Type of hypothesis: superiority
- Basis for test: continuity corrected Chi-square test
- Type I error (α): 0.05 (overall error, two-sided)
- Statistical power: 80%
- Randomization: equal allocation between S-CPR and ResQCPR treatment groups
- Interim analyses planned when 50% of the subjects were enrolled

A Fisher's Exact Test was used for analysis of the primary endpoint, with a final p-value of 0.049 required for statistical significance. It was determined *a priori* that all analyses would be performed on a mITT basis for all subjects meeting final enrollment criteria.

The original sample size calculated for the two- group mITT comparison was 1,400 subjects (700 per group). A single interim analysis was performed as proposed in the original study protocol, at the midpoint of enrollment of the two primary study arms. It was performed using the Lan-DeMets alpha spending method with O'Brien-Fleming boundaries to determine if a sample size increase would be needed to maintain statistical power to detect a significance difference between study groups, regardless of whether the difference favored the device or control arm, since the DSMB was blinded to the treatment assignment. Based upon the interim analysis, performed in March 2008, an upward sample size adjustment from 1,400 evaluable subjects to 2,696 evaluable subjects (1,348 per group) was recommended by the DSMB. Although there was an observed difference between the groups, the increase was recommended to maintain the original design objective of 80% power to detect a group difference, without knowledge of the direction of the observed difference. At the time of study termination in July

2009 (due to lack of funding as explained in **Section 7.15.5**), a total of 1,653 subjects who met final criteria had been enrolled.

7.10.4 Analysis of Secondary Safety Endpoint

All major adverse events were tracked and recorded both in the field and in the ED/hospital for purposes of assessing the secondary safety endpoint. Adverse events that occurred in the field and during transport were noted and recorded by the medics and other rescue personnel who were performing the resuscitation. Adverse events in the emergency department and hospital were tracked through hospital discharge. All adverse events, both pre-hospital and in-hospital, were included in the calculation of the event rates. A statistical analysis of this endpoint was evaluated using a test of non-inferiority for the rate of major adverse events in the ResQCPR group compared with S-CPR group. Pre-specified subgroup analyses based upon age, gender, initial recorded rhythm, time to CPR, and whether the arrest was witnessed were also performed, as well as an assessment of outcomes by study site.

7.10.5 Analysis of Secondary Effectiveness Endpoint

This secondary effectiveness endpoint was evaluated based upon CASI scores according to a hierarchical close test procedure in the following order: first, the CASI outcome evaluated at 90 days, and second, the CASI outcome was evaluated at 1 year. If statistical significance was achieved on the primary endpoint, an additional overall significance level of 0.05 would be applied to this secondary endpoint at 90 days. The CASI outcomes were evaluated in a superiority test of mean scores associated with use of the ResQCPR System versus controls using a two-group Student's t-test based on the semi-continuous CASI Score measure (scale of 0-100 points). For subjects who survived to hospital discharge (the test population for this comparison) but who died prior to the 90-day or 1-year evaluations, an imputed CASI score of zero was applied.

7.10.6 Analysis of Additional Secondary Endpoints

The secondary endpoints associated with the return of spontaneous circulation (ROSC), survival to 1 hour, ICU admission, 24 hours and 30, 90 and 365 days were compared using Fisher's Exact Tests. The secondary endpoints of neurological recovery at hospital discharge and 30, 90 and 365 days post-arrest, including the Trail Making Test, Beck Depression Inventory, CPC and OPC evaluations, and of quality of life after 365 days were compared using nonparametric Mann-Whitney U Tests. Those secondary endpoints that include an element of time (e.g., all survival outcomes) were evaluated using Kaplan-Meier actuarial analyses, with differences between treatment groups assessed for significance with log rank statistics.

Additional planned subgroup analyses for the primary and secondary endpoints included analyses based upon:

1. Witnessed vs. unwitnessed cardiac arrest
2. Those in witnessed arrest whose time from collapse to initiation of CPR is < or >10 minutes

3. Initial recorded rhythm (ventricular fibrillation/pulseless ventricular tachycardia, asystole and pulseless electrical activity), including analyses of patients who do not have asystole as a presenting rhythm, and those who are in pulseless electrical activity (PEA) at any time during the cardiac arrest.
4. Cause of death: presumed cardiac etiology, all non-traumatic, all non-cardiac
5. Subjects who, despite efforts by EMS personnel, are unable to have their airway secured with either an endotracheal tube, a Combitube or laryngeal mask airway
6. Subjects with a known 911 call to arrival of professional first rescuers of >10 minutes and no bystander CPR was being performed at the time BLS arrived
7. Gender
8. Relationship between the CASI, Trailing Making Tests, and the Beck Depression Scale, and the OPC and CPC scores.

Differences between treatment groups for these additional pre-specified secondary endpoints were evaluated using Fisher's Exact tests and Student's t-tests, but associated p-values were considered nominal and unadjusted without associated statistical significance levels. All tests were performed using StatXact, version 8 (Cytel Software, Cambridge, MA) and SPSS version 18 (SPSS, Inc., Chicago, IL) software. Continuous data were to be expressed as mean ± standard deviation.

7.11 CPR Training and Assessment

Training was provided for staff at study sites, including EMS personnel, study coordinators, and nurses responsible for conducting the neurologic follow-up evaluations (termed “neuro nurses”). Training was provided on the CPR methods deployed for the study, study protocol and CRF completion, consenting and notification of enrollment into the study, and performing the follow-up neurologic assessments.

Study CPR Methods
Study CPR trainers were designated at each site to train the EMS personnel on *both* CPR methods to be used during the study. The designated site trainers were initially trained by the Company during “Train the Trainer” sessions that consisted of lecture format presentations with discussion, videos, and written and practical exams. Rescue personnel were retrained on S-CPR per the 2005 American Heart Association Guidelines, as well as on how to use the ResQPUMP and ResQPOD. Sample refresher training materials were developed by investigators and the Company and provided to all study sites. Sites independently maintained records of initial and refresher training rosters. During the initial training and follow-up refresher sessions, skills-based competency was assessed, along with knowledge of the study and how to use study devices. A total of 4,940 EMS personnel underwent didactic and hands-on training before study enrollment started in the respective sites. Sites were encouraged to provide refresher training every six months throughout the enrollment phase. Continuing training was emphasized since an individual EMS team might treat as few as one OHCA case meeting criteria for enrollment into the study per year. As a quality assurance tool for tracking and follow-up on study cases, a research hotline was established at each site. A designated lead paramedic on the responding EMS team was instructed to contact the hotline following enrollment of a subject. To assure that both treatment arms received similar levels of care by EMS providers, quality assurance reports

were also generated using data from all non-survivors related to the duration of CPR and epinephrine usage. These reports were reviewed by the DSMB.

Site Initiation and Certification
All sites were required to complete a site initiation process in order to begin enrollment into the run-in phase of the study. Site initiation included completion of a site activation checklist, a report completed by the Company, and a formal letter notifying the site of completion of requirements for site initiation. Training items that were specified included CPR training, participant protection training, CRF completion, research hotline call-taking, and neurologic assessment training for neuro nurses. Human subject protection training was accomplished using the *Human Participants Protection Education for Research Teams,* an online course sponsored by the NIH, or an equivalent course which study staff independently completed. Certificates of completion were required, at a minimum, for the site principal investigator, study coordinator, neuro nurses, and any other study staff involved with consenting subjects. CRF completion training was provided during a site initiation visit or conference call. Training on research hotline call-taking included establishing a call-in number for each site, reviewing the recording website log-in procedures to review calls, and reviewing the call-in report form with study call-takers.

Consenting and Notification
All research staff members at the seven sites involved in the notification of subject enrollment and in consenting subjects were trained in these processes by the Company. The training included the objectives of the consent process as well as techniques and considerations when approaching subjects and families in crisis for consent.

Neurologic Assessment Training
Designated neuro nurses at each site completed training on administration and scoring of the various neurologic assessment tools that were used. Training was provided by a neuropsychologist, Dr. David Tupper, who is an expert in the field of neuro-cognitive testing.

7.12 Clinical Events Committee

An independent CEC played a key role in the study. The CEC was responsible for the adjudication of all adverse events and all subjects that the study site investigators thought may not have met the pre-specified mITT analysis criteria.

Multiple CEC meetings were held throughout the course of the study. Cases were prepared for CEC review by the Company's DCC staff in a manner which provided all relevant and/or requested information yet allowed the CEC members to remain blinded to the method of CPR treatment. The composition of the CEC remained the same for the entire duration of the study. This three member committee was comprised of an emergency room physician with expertise in toxicology, a pulmonary critical care physician, and a cardiologist.

7.13 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) reviewed safety and interim progress throughout the study. The Chairman of the DSMB was a cardiologist and the other DSMB members had expertise in bioethics, biostatistics, emergency medicine, anesthesia-critical care, neuropsychology, and cardiology. The NIH appointed an independent DSMB member, Jay Mason, M.D., a cardiologist and former Chairman of Medicine at the University of Kentucky and current Chairman of the NIH Resuscitation Outcomes Consortium DSMB. The Medical Officer from the NIH who was also administratively responsible for the study participated by telephone when possible during the DSMB meetings. The composition of the DSMB remained the same for the entire duration of the study. There were seven DSMB meetings held throughout the course of the study. The DSMB regularly reviewed aggregate summaries of study data and quality assurance reports. The DSMB provided guidance and recommendations related to continuation of the study and study conduct.

The DSMB could have requested to become unblinded to treatment assignment, or recommended stopping the trial for safety concerns, at any point. The DSMB chose to remain blinded to aggregate effectiveness and safety outcomes until July 2009, their final meeting prior to cessation of subject enrollment. Their decision to become unblinded at that time remained unknown to the Company and investigators until the study was formally unblinded in July 2010, after completion of the final 1-year follow-up on all subjects required by the study protocol.

7.14 Data Flow and Data Management

Throughout the course of the ResQTrial, the site investigators and the Company followed pre-specified, standardized procedures for obtaining, reviewing, and monitoring all data from both study arms in order to consistently and objectively record, report, and analyze the data according to the study protocol. This process began as soon as the medic called into the site coordinator through the research hotline to report a cardiac arrest, generally within minutes of finishing his or her clinical care for the subject. The site investigators gathered study outcome data from the EMS run reports, call-in reports from the medics, and hospital records. They completed the CRFs and submitted them to the Company's DCC and, unless otherwise noted, the cases were considered as meeting preliminary mITT criteria. As part of the standardized quality assurance procedures, site investigators, site coordinators and study monitors from both the sites and the DCC performed additional CRF data source verification. The DCC had a dedicated staff that verified the information on the CRFs with primary source materials, monitored individual sites multiple times to verify that all aspects of the study were implemented according to the protocol, and prepared case materials for review by the CEC.

The CEC reviewed all adverse events, and determined whether cases selected by the site investigators for review met criteria for the mITT analysis population. Those cases which met preliminary mITT criteria but not final mITT criteria, as determined by the CEC, were excluded the mITT population. The site investigators and the Company used these processes to provide standardized means to obtain high quality results.

Outcome data related to safety and effectiveness were analyzed by an independent biostatistician and provided in aggregate data tables to the DSMB in a blinded manner on a regular basis, generally annually. There were four circumstances that affected the timeline of data flow in the study, as follow:

1) *Implementation of FDA's 2008 guidance document Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials*: As described in **Section 7.5**, the implementation of FDA's 2008 updated guidance on informed consent allowed for the relatively late inclusion of data for subjects when there was a lack of a consent decision or, if consent was denied, the inclusion of data up to the point in time when consent was declined. For subjects enrolled between 2006 and 2008 for whom consent could not be obtained, adherence to the 2008 guidance may have allowed for collection of additional information that affected a subject's mRS score and inclusion or exclusion in the mITT analysis population.
2) *Timing Differences between DSMB Review and CEC Adjudication*: There were times when the CEC had not yet adjudicated some of the cases that had already been included in reports presented to the DSMB. As such, in some cases the DSMB reviewed outcome data on subjects originally presumed to be part of the mITT analysis population but who may later have been excluded because the CEC found the case had mITT exclusion criteria.
3) *Unavailable Data at Time of DSMB Review:* Data elements were unknown or unconfirmed on a limited number of subjects when the DSMB was provided with their interim reports. For example, a patient may have still been in the hospital when an interim DSMB report was prepared. Consequently, their discharge status was unknown. Subsequent data collection efforts may have resulted in more complete data being available after initial inclusion of a case in a DSMB report.
4) *Monitoring Activities:* Corrections to collected study data could have occurred based on monitoring and query activities. Prescribed monitoring activities occurred through the end of the ResQTrial, even after new subject enrollment was discontinued, and sometimes resulted in data corrections months or years after a subject's initial enrollment.

These circumstances, which were anticipated given the challenges associated with out of hospital cardiac arrest research, created the potential for collection of additional information that changed the mITT assignment and/or mRS score for certain subjects during the study, sometimes months or years after the patient's initial enrollment. These changes were made in a uniform manner for all study subjects and study groups and were consistent with FDA guidance. Post hoc sensitivity analyses, as shown in **Section 8.9.7.6**, demonstrated that these changes occurred in only a limited number of subjects and had no significant impact on overall study outcomes.

7.15 Chronology of Events Related to Study Design/Analysis

A study timeline, shown in **Figure 7.1**, provides the dates of the key events that took place during the course of the study. Enrollment is shown on a quarterly basis and the number of subjects enrolled who met criteria for mITT analysis are shown in parentheses.

The initial NIH grant for the ResQTrial was awarded in February 2005, the first subject was enrolled in the run-in phase in October 2005, and the one year follow-up on the last subject enrolled was completed in July 2010. As shown in the timeline, during the course of the study, two additional study sties were added to accelerate enrollment rates. Additional study design and analysis events are outlined in the chronology and described below.

Figure 7.1 Chronology of ResQTrial Events

	Quarter (mITT enrollment)	KEY EVENT
2005	Q1 (0)	Initial NIH funding awarded
	Q2 (0)	FDA approved IDE for enrollment of 1,400 subjects
	Q3 (0)	
	Q4 (0)	Sites enrolled first run-in phase subject
2006	Q1 (11)	Sites enrolled first pivotal phase subject
	Q2 (80)	FDA approved inclusion of medication/drug overdoses in mITT
	Q3 (158)	
	Q4 (240)	
2007	Q1 (342)	
	Q2 (418)	
	Q3 (505)	3rd study arm (S-CPR + ResQPOD alone) was discontinued
	Q4 (623)	Site 6 began pivotal phase enrollment
2008	Q1 (784)	Additional NIH funding awarded
	Q2 (942)	
	Q3 (1071)	Study was resized to enrollment of 1348 subjects per study arm based on DSMB recommendation after interim analysis was performed per protocol,
	Q4 (1247)	FDA guidance *Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials* released
2009	Q1 (1420)	Implementation of updated FDA 50.24 guidance began
	Q2 (1608)	Site 7 began pivotal phase enrollment
	Q3 (1655)	DSMB was unblinded, new NIH application not funded and new subject enrollment was suspended
	Q4 (1655)	
2010	Q1 (1655)	Second new NIH application not funded and new subject enrollment was permanently stopped
	Q2 (1655)	
	Q3 (1655)	1 year follow-up on all subjects was completed and Sponsor was unblinded

7.15.1 Medication and Drug Overdose Cases

The study was designed to focus on subjects in cardiac arrest of cardiac etiology. Subjects with an arrest secondary to medication or drug overdose (OD) were initially excluded from the primary mITT analysis population. This subgroup has traditionally not been included in cardiac arrest trials as cardiac arrests due to medication and drug OD generally have poor prognoses.[9] The investigators and Company considered whether it would be possible to resuscitate more of these subjects if flow to the heart and brain could be increased along with administration of drugs that might help reverse the effects of the metabolic abnormalities and drug overdoses. As such, the investigators and Company made a request to the FDA on April 20, 2006, for permission to include subjects with medication or drug overdoses in the primary analysis population to provide a better picture of whether the devices may be helpful in this subject population. On May 2, 2006, FDA approved the request but indicated the Company would not be able to expand the Indications for Use unless there were an adequate number of subjects in this subgroup to support an evaluation.

The Investigational Plan was modified to include the medication/drug OD patients in the mITT Inclusion criteria, but, given the uncertainty of having enough subjects in this subgroup at the end of the study to assess safety and efficacy, the sites continued to identify medication/drug OD subjects for adjudication by the CEC and the CEC continued to exclude the medication/drug OD subjects for the entire duration of the study. In addition, this subgroup was not included in the interim analysis or any DSMB reports pending determination of the number of subjects in this subgroup. Prior to unblinding, the FDA was notified there were insufficient subjects to assess ResQCPR effect in this subgroup and therefore subjects with medication and drug overdoses were not included in the primary mITT analysis (though they remained in the full ITT analysis).

7.15.2 Discontinuation of the Third Study Arm (S-CPR+ITD)

The original study protocol included a third study arm, treatment with S-CPR plus the ITD alone. The original protocol specified that one subject was to be enrolled in this third arm for every two subjects in the S-CPR and ResQCPR groups until statistical significance was achieved between the S-CPR and ResQCPR study groups. However, the S-CPR+ITD study arm was discontinued in November 2007 primarily to focus all available limited resources on the primary study objective, namely, the comparison between S-CPR and ResQCPR. Discontinuation of the third arm was also intended to reduce the potential for randomization errors and protocol violations. The Company and DSMB were blinded to the results of the third arm when the recommendation was made by the DSMB to discontinue enrollment in that arm. FDA approved the discontinuation of the third study arm.

7.15.3 Resizing of Study after the Interim Midpoint Analysis

As described in **Section 7.10.3**, a pre-planned single interim analysis resulted in a recommendation by the DSMB to increase the sample size in the S-CPR and ResQCPR study arms from 700 subjects per arm to 1,348 subjects per arm in the mITT population. While the study showed a difference between groups at the time of the interim analysis, the difference was

not as large as initially projected in the original sample size calculations. The recommended increase in sample size was implemented in order to maintain the original 80% statistical study power level planned for the study to detect a significant difference between study groups. Although the resizing of the study was implemented in December 2008, a post-hoc analysis requested by FDA (described in **Section 8.9.7.6**) demonstrates the study would have achieved statistical significance if it had not been resized and the original enrollment target had been maintained.

7.15.4 Release of the 2008 FDA Guidance Document

As described in **Section 7.5**, the FDA issued additional guidance in October 2008 concerning the gathering of outcome data when there was a lack of a consent decision or consent was denied. The implementation of this updated guidance began in early 2009 and resulted in the relatively late review and exclusion of some subjects from the ResQTrial mITT analysis population; up to months or years after their arrest in some cases. **Section 8.9.7.6** provides detail of a post-hoc analysis that demonstrates that the implementation of this guidance did not have a significant effect on the primary outcome results of the study.

7.15.5 Early Discontinuation of Study Enrollment

The study was primarily funded by the NIH through a Small Business Innovation Research (SBIR) award. The NIH provided the first grant to the Company in February 2005 and a second grant in February 2008 to help fund full enrollment of the original study size of 1,400 patients. The resizing of the study to 1,348 subjects per arm (2,698 total) in December 2008 resulted in the need for significantly more funding and the Company thus applied for additional funding from the NIH. The NIH denied this funding request in July 2009, but recommended that the Company re-apply for the additional funding through a different NIH process. As a result, the Company did not have sufficient funding in place as of July 2009 to complete full patient enrollment in the study. Based on this funding shortfall and DSMB guidance that patient enrollment should continue only if adequate funding was in place to achieve the full enrollment target, the Company suspended new subject enrollment in July 2009 and re-applied for additional NIH funding. At that time the Company also sought additional investors to complete the study. Despite receiving an excellent study score, on April 5, 2010, the Company received notification that the second NIH grant application for additional funding was not approved. The Company was also unsuccessful at raising additional non-governmental funds for the ResQTrial. Immediately thereafter, the Company permanently terminated new subject enrollment due to lack of sufficient funds and instructed the investigators to complete any remaining 1-year follow-up assessments per the study protocol. At that time, aggregate unblinded study results were unknown to the Company and the investigators.

On May 21, 2010, the Company and FDA agreed on a plan to complete all follow-up visits for all applicable enrolled subjects, to complete all data quality assurance activities prior to locking the study database, and to then un-blind the data. The Company agreed to perform the final analyses as outlined in the study Statistical Analysis Plan, and report the findings to FDA. It was agreed that if the study results were found to be unfavorable or equivocal with regard to the investigational device, the Company would file a final IDE report with FDA and not pursue a

PMA application. If the results were favorable to the investigational device, the Company would then notify FDA of its intent to seek PMA approval, which is eventually what occurred. The final subject was enrolled on July 29, 2009, and the 1-year follow-up assessments were completed in July 2010.

7.16 Changes in the Study Device

The ResQPOD ITD included timing lights that were used for guidance in providing ventilations at the recommended rate during CPR. Six months after the start of the study, the AHA changed the recommended ventilation rate from approximately 12 breaths per minute to 8-10 breaths per minute. A version 1 model of ResQPOD was initially used in the study in a limited number of subjects receiving ResQCPR. The timing lights in version 1 were set at a rate of 12 flashes per minute, in accordance with the then-AHA recommended ventilation rate. Following the change in the AHA recommended ventilation rate, design changes were made to the ResQPOD resulting in a version 2 with timing lights set at rate of 10 flashes per minute. These design changes did not affect the primary inspiratory impedance function of the ResQPOD. The overall rate of use of version 1 in the pivotal study phase was low (version 1 was used in only 1.1% of subjects in the ITT population) and the poolability of clinical results using both models was considered justified.

8 PIVOTAL STUDY RESULTS

8.1 Enrollment and Accountability

8.1.1 Enrollment in Run-In Phase

Run-in phase enrollment started in October 2005. A total of 599 subjects were screened and assigned a case number. Of these, 331 were screen failures, meaning they did not receive CPR due to obvious signs of clinical death or had a traumatic arrest, and were not randomized to S-CPR or the ResQCPR System. A total of 268 subjects met selection criteria for the ITT study population and 197 for the mITT analysis. Survival up to one year, adverse events and complications were monitored and reported to the DSMB according to the Investigational Plan.

8.1.2 Enrollment in Pivotal Phase

Enrollment by site for the pivotal phase is shown in **Table 8.1**. Pivotal phase enrollment began in March 2006 and was terminated in July 2009. A total of 5,267 subjects were screened and assigned a case number. A total of 2,470 subjects met the initial selection criteria and were randomized and included in the study. A total of 2,797 were screen failures for the pre-specified following reasons: known or presumed to be <18 years of age (129); cardiac arrest of likely traumatic or non-cardiac etiology (270); pre-existing 'do not resuscitate' orders (150); signs of obvious clinical death or condition that precluded the use of CPR (2,190); family or legal representatives request that subject not be entered into study (2); in-hospital cardiac arrest (3); recent sternotomy (6); prisoner (22); presumed cardiac arrest but resuscitated without EMS CPR (23), and re-arrest within 365 days (2).

Table 8.1 Pivotal Phase Enrollment by Site in ITT Population

Site	Location	Principal Investigator	Phase duration[1]	Receiving hospitals	Subjects enrolled
01	Saint Paul, Minnesota	Ralph Frascone MD	2/27/06 to 7/29/09	6	359
02	Minneapolis, Minnesota	Brian Mahoney MD	5/27/06 to 7/28/09	7	532
03	Whatcom County, Washington	Marv Wayne MD	4/16/06 to 7/27/09	1	340
04	Beaumont Health System, Michigan	Robert Swor DO	4/2/06 to 7/3/09	7	523
05	Oshkosh, Wisconsin	Tom Aufderheide MD	2/26/06 to 7/20/09	2	106
06	Ann Arbor, Michigan	Robert Domeier MD	12/18/07 to 7/29/09	8	469
07	Indianapolis, Indiana	Michael Olinger MD	4/10/09 to 7/28/09	9	141
TOTAL				40	2470

[1]"Phase duration" includes dates of first and last enrollment. Abbreviations: ITT= intention-to-treat population

8.2 Analysis Populations

The ITT (intention-to-treat) population consisted of all subjects in presumed non-traumatic arrest who were randomized and treated by EMS personnel with either S-CPR or ResQCPR. A total of 2470 subjects were included in the ITT population: 1269 in the ResQCPR group and 1201 in the S-CPR group.

The protocol-specified primary analysis population for the pivotal study was the modified intention-to-treat (mITT) population. These were subjects enrolled in the pivotal phase ITT population who also met all mITT selection criteria and did not have any exclusionary criteria, as described in **Section 7.3**.

8.2.1 Subject Accountability at Follow-Up

Subject accountability by site for the hospital discharge, 30-day, 90-day, and 1-year follow-up intervals is shown in **Table 8.2** and **Table 8.3** for subjects randomized to either S-CPR or ResQCPR during the pivotal phase.

Table 8.2 Subject Accountability in Pivotal Phase Through Hospital Discharge*

		Hospital Discharge[1]		
Outcome by analysis group	Subjects	Died pre-hospital or in-hospital	Discharged alive	Neurological status evaluated
ITT (mITT)[2]	**2470** (1655)	**2186** (1462)	**273** (185)	**262** (176)

*For subjects who withdrew from the study, a public death record search was performed 1 year after cardiac arrest. If a death record was found, the date of death was used to determine the subject's status at the appropriate follow-up intervals. If no death record was found, survival status was listed as unknown.
[1] Hospital discharge status could not be obtained in 13 subjects and neurological evaluations were not obtainable in 11 subjects.
[2]Subjects who met mITT analysis criteria are shown in parentheses.

Table 8.3 Subject Accountability in Pivotal Phase After Hospital Discharge*

	30 Days[1]			**90 Days[2]**			**1-Year[3]**		
Outcome by analysis group	Died after discharge & before 30 days	Alive	Follow-up performed	Died after 30 days & before 90 days	Alive	Follow-up performed	Died after 90 days & before 1 year	Alive	Follow-up performed
ITT (mITT)[4]	**24** (18)	**229** (161)	**196** (143)	**9** (7)	**204** (145)	**175** (127)	**22** (8)	**164** (122)	**143** (110)

*For subjects who withdrew from the study, a public death record search was performed 1 year after cardiac arrest. If a death record was found, the date of death was used to determine the subject's status at the appropriate follow-up intervals. If no death record was found, survival status was listed as unknown.
[1]Survival to 30 days could not be obtained in 32 subjects and neurological evaluations were not obtainable 65 in subjects.
[2]Survival to 90 days could not be obtained in 48 subjects and neurological evaluations were not obtainable 77 in subjects.
[3]Survival to 365 days could not be obtained in 66 subjects and neurological evaluations were not obtainable 86 in subjects.
[4]Subjects who met mITT analysis criteria are shown in parentheses.

Subject accountability in the ITT pivotal phase population, from the time of the initial screening for enrollment by EMS personnel to randomized treatment in the field for the two main study arms, is shown in **Figure 8.1**.

Figure 8.1 Subject Accountability to Enrollment (Pivotal Phase)

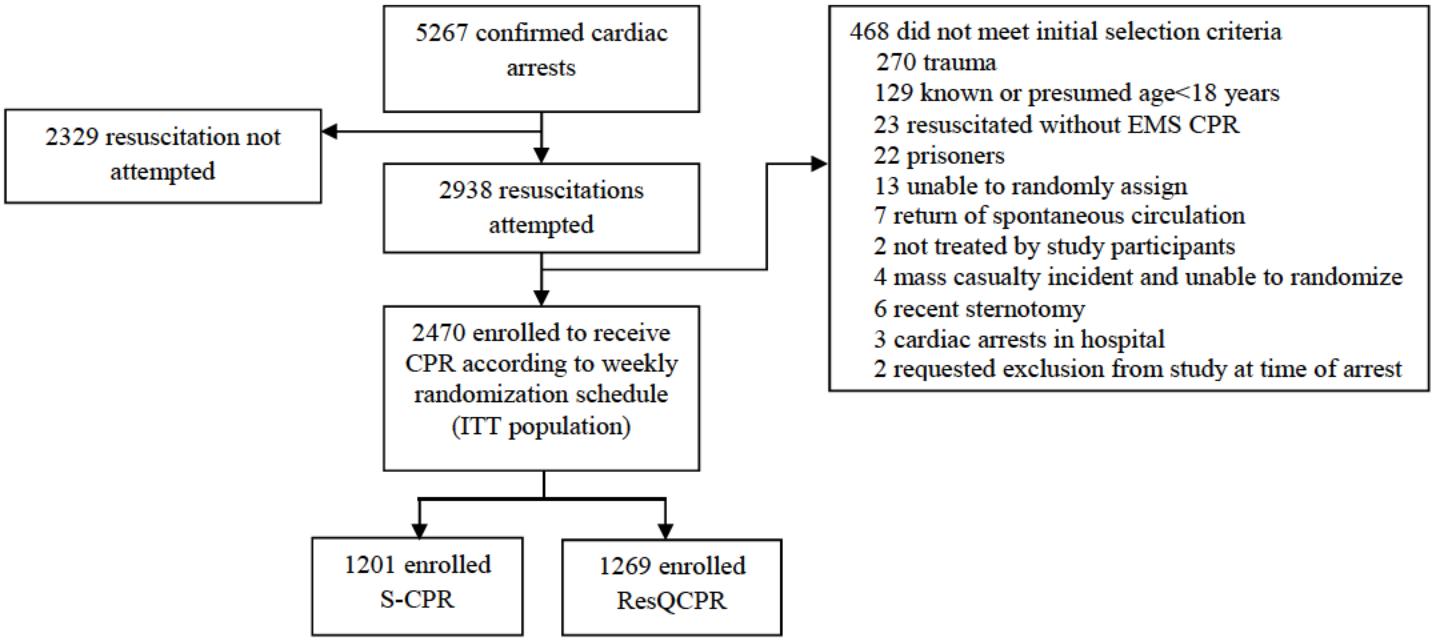
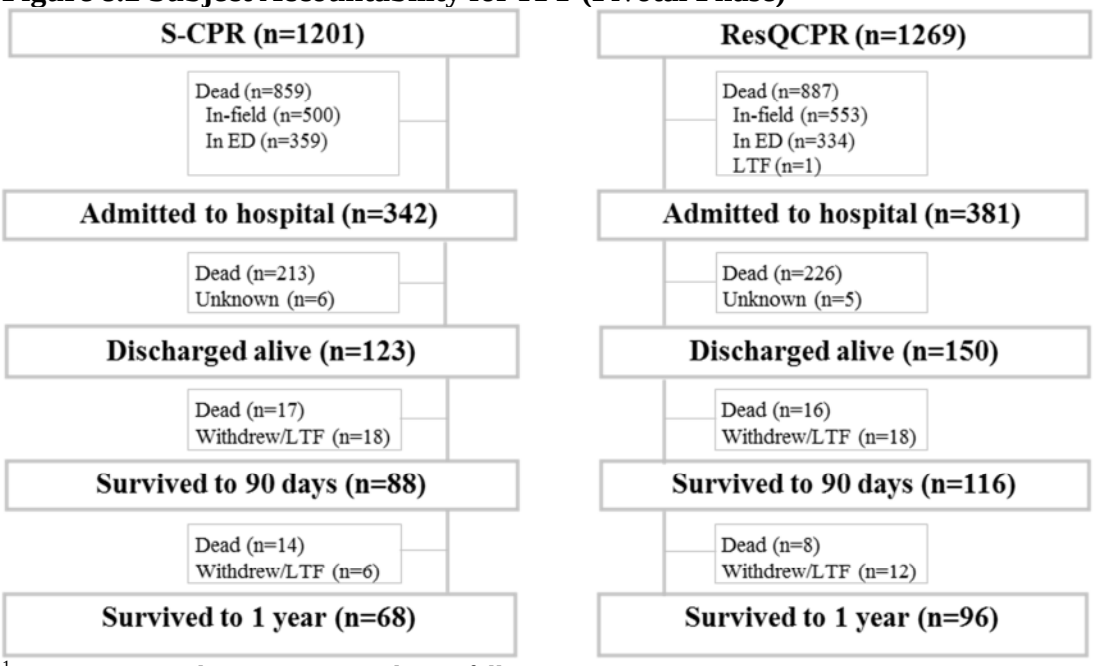
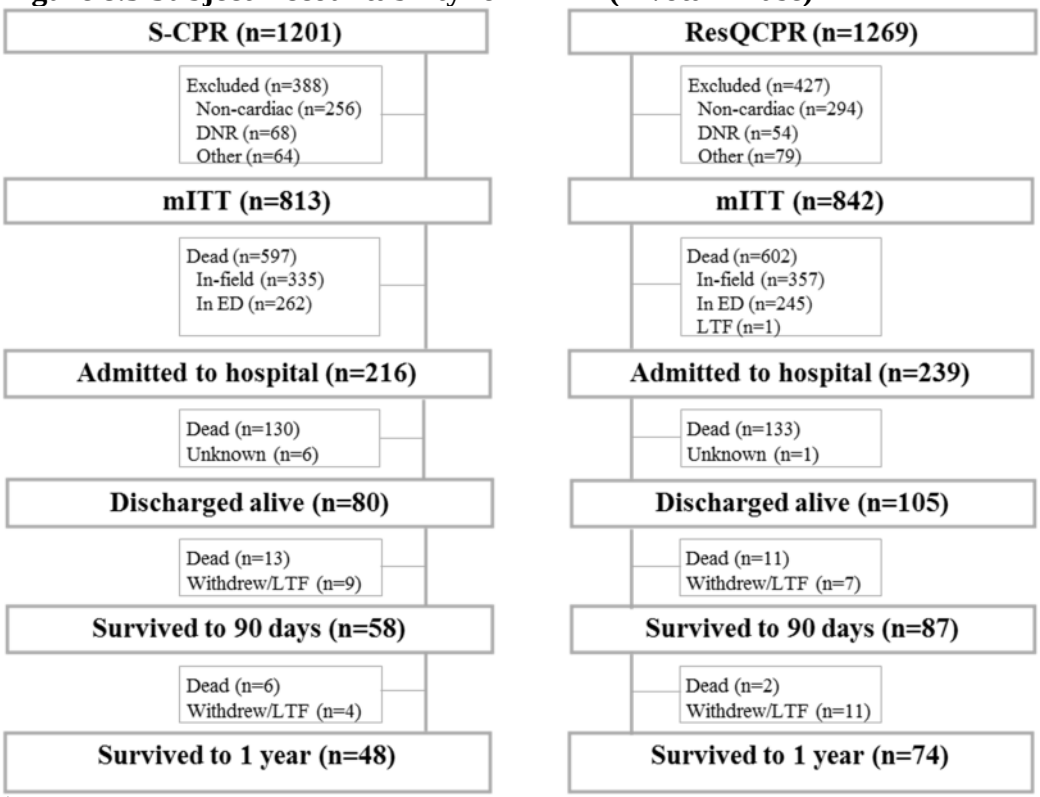


Figure 8.2 Subject Accountability for ITT (Pivotal Phase)[1]



[1]ED= emergency department, LTF= lost to follow-up

Figure 8.3 Subject Accountability for mITT (Pivotal Phase)[1]



[1]ED= emergency department, LTF= lost to follow-up

8.3 Study Administration Issues

8.3.1 Protocol Deviations during Pivotal Study

Major and minor protocol deviations in the pivotal study were tracked throughout the study and are shown in **Table 8.4** for the ITT population and in **Table 8.5** for subjects who met criteria for the mITT analysis. Major deviations were defined as those cases that may have impacted the assessment of the primary endpoint. Minor deviations did not have the potential to affect the primary study endpoint results directly.

Table 8.4 Protocol Deviations, Pivotal Phase, ITT Population [N=2470 enrolled in S-CPR and ResQCPR study groups]

	Subjects
Total number enrolled	2470
Major protocol deviations (% of enrolled subjects)	291(11.8)
Major Protocol Deviations, by category	
1. Failure to apply devices within 2 minutes of CPR start	94
2. Randomization error	36
3. ITD not removed upon ROSC	60
4. Failure to discontinue ITD use after it fills with fluid ≥2 times	2
5. Failure to reapply devices immediately upon re-arrest	4
6. Other improper use of device (not included in 1-5 above)	95
Minor Deviations	
1. Failure to contact hotline	174
2. Reviewed medical records prior to obtaining consent	19
3. Follow-up completed outside designated window	217

Table 8.5 Protocol Deviations, Pivotal Phase, mITT Population [N=1655 enrolled in S-CPR and ResQCPR study groups]

	Subjects
Total number enrolled	1655
Major protocol deviations (% of enrolled subjects)	182 (11.0)
Major Protocol Deviations	
1. Failure to apply devices within 2 minutes of CPR start	68
2. Randomization error	21
3. ITD not removed upon ROSC	43
4. Failure to discontinue ITD use after it fills with fluid ≥2 times	1
5. Failure to reapply devices immediately upon re-arrest	2
6. Other improper use of device (not included in 1-5 above)	47
Minor Deviations	
1. Failure to contact hotline	104
2. Reviewed medical records prior to obtaining consent	13
3. Follow-up completed outside designated window	143

None of the protocol major or minor deviations resulted in the exclusion of subjects from the main ITT and mITT study analyses. However, subjects with certain major protocol deviations

were excluded from the per protocol analysis (e.g., 10 S-CPR subjects who had investigational devices used and 43 ResQCPR subjects where protocol deviations were reported indicating that one or both study devices were not used and should have been).

Major protocol deviations included randomization errors which were defined as "failure to stock the emergency response vehicles with the correct study CPR devices, in accordance with the weekly randomization schedule for the study site." This included: (i) failure to stock the vehicles with the ResQPUMP and ResQPOD during a ResQCPR week such that these devices were not available for use at the scene; or (ii) failure to remove these study devices during a S-CPR week, such that subjects were treated with these devices when they should not have been, according to the randomization schedule. During the pivotal phase there were 17 cases in the ITT group (11 of the cases were included in the mITT analysis population) where one or more study devices were not available to use when they were supposed to be. There were 19 cases in the ITT population (10 of the cases were included in the mITT analysis) where one or more devices should not have been available but were used on a subject. The category "other improper use of devices (not included in 1-5 above)" included circumstances when study devices were available and should have been used but were not, such as when EMS personnel forgot to use devices, devices were not brought to the patient as the 911 call-for-help suggested the subject was not in cardiac arrest, or the medic did not think it was appropriate to use devices (e.g., subject had non-traumatic hypovolemia).

Minor deviations included "follow-up completed outside designated window"; this category accounted for more minor deviations than any other category often due to an inability to contact a subject, despite diligent attempts to do so, in order to schedule an appointment within the specified window. The follow-up windows as defined in the protocol were 30 ± 5 days, 90 ± 5 days, and 365 ± 15 days, and were thus relatively restrictive. When applying more reasonable and less restrictive follow–up windows (e.g., 30 ± 14 days, 90 ± 14 days, and 365 ± 30 days), the percent of deviations due to follow-ups performed outside the window were reduced from 41.2% (217/527) to 20.9% (82/392) of the total deviations. Failure to contact the hotline was a minor protocol deviation. Importantly, failure to contact the hotline did not pose any increased risks to the subject as the hotline was called after the investigational devices were evaluated to assure protocol compliance. Failure to call the hotline prevented an immediate downloading of information related to possible device and protocol issues.

There were ongoing efforts throughout the study to reduce the number of protocol deviations. The Company contacted the principal investigators or designated study coordinator immediately after learning of any new major protocol deviations to determine the root cause of the deviation and implement a corrective action, as applicable. Other actions that were taken to reduce protocol deviations included the following: a) research team contacted the Company within one day as well as all involved crew members following every randomization error to provide further education and remediation in a timely manner, b) quarterly publications of a newsletter containing important study updates for all EMS personnel, c) ongoing refresher training throughout the study, d) self-directed training programs in all sites, e) regular investigator meeting to discuss study compliance issues, f) sites were required to submit routine reports to the Company detailing enrollment and any protocol deviations, including overdue case report forms, and g) a study monitor visited each site periodically to assess the quality of CPR performance

with and without investigational devices, and assessed whether practices were in place to reduce or eliminate protocol deviations and randomization errors.

The multiple actions described above resulted in minimizing the protocol deviations and responsibly managing those that did occur. Overall, protocol deviations in this complex study were kept at a minimum given the over 4,000 first responders and 46 EMS agencies involved in the study.

8.3.2 Study Enrollment under 21 CFR § 50.24

As described above, the study was conducted under the regulation 21 CFR § 50.24: *Exception from Informed Consent Requirements for Emergency Research*. Unlike many non-cardiac arrest clinical trials, the vast majority of subjects entered into the ResQTrial died prior to hospital discharge. Those that survived were often comatose for a number of days following the arrest. Some survivors were discharged back into the community and were not interested in participating for up to a year in the trial, and others were lost to follow-up. Taken together, these circumstances presented a unique set of challenges associated with the exception from informed consent process, including the need to work closely with the subject‘s legally authorized representatives to access the subject’s medical records, inherent time delays between the arrest and when consent could be obtained, and the potential for resultant delays in gathering primary outcome data and follow-up outcome data. Ultimately, outcome data were available for analysis of the primary study endpoint in 800/813 (98.4%) subjects treated with S-CPR and 838/842 (99.5%) subjects treated with ResQCPR. This is a high percentage for this complex exception from informed consent study.

8.3.3 Clinical Events Committee Adjudication

The Clinical Events Committee (CEC) determined that a total of 815 pivotal phase cases from the ITT population did not meet the mITT analysis criteria, as shown in **Table 8.6**. Of these, 550 were adjudicated as having a cardiac arrest of presumed non-cardiac etiology. Findings related to the different non-cardiac etiologies are described in **Table 8.7**.

Table 8.6 CEC Adjudication of Cases Not Meeting mITT Criteria

Criteria for Exclusion from mITT Population[1]	Pivotal Phase	
	S-CPR (n=388)	ResQCPR (n=427)
< 18 years old	0	1
Presumed non-cardiac etiology *(see Table 8.6)*	256	294
Leaky or uncuffed advanced airway (includes pre-existing stoma, tracheotomy, or tracheostomy)	12	21
Pre-existing DNR orders (includes having efforts terminated prematurely)	68	54
Signs of obvious clinical death/ conditions that preclude the use of CPR	23	22
Recent sternotomy	3	3
Prisoner (Sites 01,02,05,06)	1	1
Unable to clear airway obstruction (includes inability to place advanced airway)	17	18
Received < 1 minute of CPR	8	13
TOTAL (% of subjects enrolled)	**388/1201 (32.3%)**	**427/1269 (33.6%)**

[1] Subjects randomized to ResQCPR or S-CPR in the pivotal phase were excluded from the mITT analysis population if any of the listed exclusion criteria were present.

Table 8.7 CEC Adjudication of OHCA Due to Presumed Non-Cardiac Etiology

Arrest Etiology (non-cardiac)	Pivotal Phase	
	S-CPR (n=256)	ResQCPR (n=294)
Burns	0 (0.0)	1 (0.3)
Cerebral bleed (includes CVA, stroke, cerebral hemorrhage/aneurysm, subdural hematoma, subarachnoid hemorrhage)	11 (4.3)	8 (2.7)
Drowning	4 (1.6)	4 (1.4)
Hyperthermia	1 (0.4)	0 (0.0)
Hypothermia	1 (0.4)	1 (0.3)
Metabolic	12 (4.7)	17 (5.8)
Overdose	65 (25.4)	98 (33.3)
Respiratory (excluding PE)	64 (25.0)	71 (24.1)
Seizure	10 (3.9)	6 (2.0)
Smoke	0 (0.0)	0 (0.0)
Trauma	3 (1.2)	10 (3.4)
Other[1]	85 (33.2)	78 (26.5)

[1] "Other" in pivotal phase included: AIDS (1), acute pancreatitis (1), anaphylaxis/allergic reaction (2), aortic aneurysm/dissection (14), autoimmune disease (1), cancer (31), carbon monoxide toxicity (7), electrocution (3), head injury (1), hypovolemia (44), liver failure (3), meningitis (1), organ rejection (1), pulmonary embolism (35), pulmonary hypertension (1), renal failure (3), sepsis (12). There were 2 etiologies reported as other, cerebral bleed (1) and metabolic (1). These are both counted in the "other" category as reported by the site.

8.4 Demographics and Baseline Information

Baseline characteristics, demographics and pre-hospital resuscitation efforts are shown in **Table 8.8** (ITT population) and **Table 8.9** (mITT population). The baseline characteristics, demographics and pre-hospital resuscitation efforts were balanced between the two treatment arms for subjects in the ITT population and those who met mITT analysis criteria.

Table 8.8 Baseline Characteristics (ITT)[1]

Parameter	S-CPR (N=1201)	ResQCPR (N=1269)
Age, years (mean ± SD)	64.22 ± 17.19	63.34 ± 17.78
15-24 years	23 (1.9)	27 (2.1)
25-34 years	42 (3.5)	56 (4.4)
35-44 years	89 (7.4)	114 (9.0)
45-54 years	178 (14.8)	211 (16.6)
55-64 years	273 (22.7)	234 (18.5)
65-74 years	224 (18.7)	224 (17.7)
75-84 years	218 (18.2)	253 (20.0)
≥85 years	154 (12.8)	149 (11.8)
Not available	0	1
Male	752 (62.6)	803 (63.3)
Race		
White	960 (79.9)	1035 (81.6)
Asian	39 (3.2)	29 (2.3)
Native Hawaiian/Pacific Islander	4 (0.3)	1 (0.1)
American Indian/Alaska Native	18 (1.5)	22 (1.7)
Black/African American	152 (12.7)	155 (12.2)
Not available	28 (2.3)	26 (2.1)
Ethnicity		
Hispanic/Latino	22 (1.8)	32 (2.5)
Not Hispanic/Latino	1149 (95.7)	1207 (95.2)
Not available	30 (2.5)	29 (2.3)
Bystander witnessed arrest	517 (43.1)	546 (43.2)
EMS witnessed arrest	146 (12.2)	144 (11.4)
Unwitnessed arrest	536 (44.7)	575 (45.5)
Not available	2	4
First CPR performed by:		
Bystander	489 (40.7)	532 (42.0)
EMS	711 (59.2)	735 (58.0)
Not available	1	2
Initial arrest rhythm:		
Ventricular fibrillation/pulseless ventricular tachycardia	294 (24.5)	335 (26.4)
Asystole	597 (49.7)	633 (49.9)
Pulseless electrical activity	293 (24.4)	284 (22.4)
Not available	17	16
911- to- first response, minutes (mean ± SD)	5.3 ± 2.8	5.3 ± 2.8
911-to- EMS CPR, minutes[2] (mean ± SD)	6.7 ± 3.5	6.7 ± 3.2
911-to-first study device placed, minutes[2] (mean ± SD)	-	7.1 ± 3.5

[1]Numbers shown are subjects (%), unless otherwise indicated.
[2]Data do not include arrests witnessed by EMS personnel.

Table 8.9 Baseline Characteristics (mITT)[1]

Parameter	S-CPR (N=813)	RESQCPR (N=842)
Age, years (mean ± SD)	66.8 ± 14.5	67.0 ± 15.2
15-24 years	1 (0.1)	3 (0.4)
25-34 years	11 (1.4)	8 (1.0)
35-44 years	36 (4.4)	47 (5.6)
45-54 years	114 (14.0)	133 (15.8)
55-64 years	215 (26.4)	180 (21.4)
65-74 years	172 (21.2)	169 (20.1)
75-84 years	162 (19.9)	192 (22.8)
≥85 years	102 (12.5)	110 (13.1)
Male	539 (66.3)	559 (66.4)
Race:		
White	660 (81.2)	715 (84.9)
Asian	31 (3.8)	19 (2.3)
Native Hawaiian/ Pacific Islander	3 (0.4)	1 (0.1)
American Indian/Alaska Native	9 (1.1)	10 (1.2)
Black/African American	94 (11.6)	88 (10.5)
Unknown	16 (2.0)	9 (1.1)
Ethnicity:		
Hispanic/Latino	15 (1.8)	19 (2.3)
Not Hispanic/Latino	782 (96.2)	811 (96.3)
Unknown	16 (2.0)	12 (1.4)
Bystander witnessed arrest	383 (47.2)	400 (47.5)
EMS witnessed arrest	76 (9.4)	80 (9.5)
Unwitnessed arrest	353 (43.5)	361 (42.9)
Not available	1 (0.1)	1 (0.1)
Bystander CPR	350 (43.1)	358 (42.5)
Not available	1 (0.1)	0 (0.0)
Initial arrest rhythm:		
Ventricular fibrillation/pulseless ventricular tachycardia	247 (30.4)	292 (34.7)
Asystole	379 (46.6)	376 (44.7)
Pulseless electrical activity	180 (22.1)	171 (20.3)
Not available	7 (0.9)	3 (0.4)
911- to- first response, minutes (mean ± SD)	5.3 ± 2.8	5.3 ± 3.0
911-to- EMS CPR, minutes (mean ± SD)[2]	6.6 ± 3.4	6.7 ± 3.2
911-to- first study device placed, minutes (mean ± SD)[2]	-	7.1 ± 3.5

[1]Numbers shown are subjects (%), unless otherwise indicated.
[2]Data do not include arrests witnessed by EMS personnel.

8.5 Device Use

A summary of the duration of treatment for all subjects treated with the ITD and ACD-CPR device, the percentage of time each airway adjunct was used with the ITD, and the number of times and why suction was reported as difficult to obtain during ACD-CPR, is provided in **Table 8.10**. In the mITT analysis group, there were 82 cases (9.7% of all subjects randomized to ResQCPR) where difficulty with suction was reported; however, use of the device was continued for the entire duration of CPR in 74/82 (90%) of these cases as it could be used to deliver chest compressions without any reported untoward consequences.

Table 8.10 Summary of ResQCPR Treatment[1]

	ITT (n=1269)	mITT (n= 842)
ITD treatment duration, minutes (Mean ± SD)	26.8 ± 12.4	28.1 ± 12.1
≤ 1 min	14 (1.1)	6 (0.7)
>1 min and ≤ 5 min	56 (4.4)	24 (2.9)
> 5 min and ≤ 10 min	75 (5.9)	46 (5.5)
> 10 min and ≤ 20 min	190 (15.0)	118 (14.0)
> 20 min and ≤ 30 min	376 (29.6)	271 (32.2)
> 30 min	443 (34.9)	329 (39.1)
Not available/not applicable[2]	115 (9.1)	48 (5.7)
ACD-CPR treatment duration, minutes (Mean +/- SD)	26.4 ± 12.1	27.9 ± 11.6
≤ 1 min	12 (0.9)	2 (0.2)
>1 min and ≤ 5 min	58 (4.6)	24 (2.9)
> 5 min and ≤ 10 min	81 (6.4)	43 (5.1)
> 10 min and ≤ 20 min	208 (16.4)	137 (16.3)
> 20 min and ≤ 30 min	372 (29.3)	263 (31.2)
> 30 min	457 (36.0)	339 (40.3)
Not available/not applicable[3]	81 (6.4)	34 (4.0)
ITD attachment-		
To facemask	1028	718
To endotracheal tube	813	588
To supraglottic airway (e.g., combitube, laryngeal mask airway)	227	169
ACD-CPR device-		
Suction difficulty	118 (9.3)	82 (9.7)
Device use discontinued	14	8
due to:		
breast size	14	10
hair	15	14
diaphoresis	24	16
chest shape	19	14
other/unknown	58	40

[1]Data shown are number of subjects (%). Periods of return of spontaneous circulation (ROSC) were factored out of all device durations shown in the table; therefore, the duration represents only time the device was actually in use.
[2]Subjects did not receive the ITD despite being randomized to the ResQCPR group.
[3]Subjects did not receive ACD-CPR despite being randomized to ResQCPR group.

8.6 Study Device Failures

ResQPUMP and ResQPOD device failures that were reported during the pivotal study phase are summarized in **Table 8.11**. All device failures were adjudicated by the CEC. No device failures resulted in suspension of CPR treatment or adversely affected patient care.

Table 8.11 ResQPOD and ResQPUMP Device Failures Among Subjects Treated with ResQCPR in the ITT Population and Those Who Met Criteria for mITT Analysis

	ITT (n=1269)	mITT (n=842)
ResQPOD device failure[1]*:*		
timing light	87	60
male adaptor of BVM broke off, lodged within device	1	1
difficult ventilation using device, unspecified	1	1
ResQPOD Failure Rate per subject, overall	90/1269 (7.1%)	62/842 (7.4%)
ResQPOD Failure adversely affecting patient care	0	0
ResQPUMP device failure:		
force gauge	2	2
metronome	13	9
suction cup detachment	1	1
ResQPUMP Failure Rate per subject, overall	16/1269 (1.3%)	12/842 (1.4%)
ResQPUMP failure adversely affecting patient care	0	0

[1] There were 62 ResQPOD device failures that occurred in 60 subjects enrolled to ResQCPR in the primary analysis population. In one subject, there were 2 reports of timing light failure in 2 different devices that were used. In another subject, there was 1 report of timing light failure and another report of difficult ventilation.

There were a total of 87 reports of the timing assist lights failing to function as intended. The timing lights were incorporated in the ResQPOD to provide a means to guide rescuers in the proper ventilation rate. The timing lights were completely independent of the device's primary function of providing inspiratory impedance and thereby augmenting circulation. In the event of timing light failures, EMS personnel used another device or ventilated as they had been trained to do. The ResQPOD Directions for Use contained the following guidance in this regard: "If timing assist lights fail to operate or appear to blink at a rate different than 10/minute, discontinue their use and ventilate at 10/minute (once every 6 seconds)."

There were 16 device-related incidents with the ResQPUMP reported during the study: two were described as the force gauge not functioning properly, 13 were related to the ResQPUMP metronome, and one was related to the suction cup detaching from the handle of the ResQPUMP. In one case of metronome failure, it was determined by the site that the device was likely not cleaned appropriately and this caused the battery contacts to become corroded. In the other cases, the metronome failure could not be replicated and it is was likely that the reported failures were due to an automatic shut-off feature of the ResQPUMP in which the metronome turns off after 10 minutes regardless of whether the pump is being used or not. Upon further review and discussion with the study site, it was concluded that the medics may have forgotten this feature and believed that the metronome had malfunctioned. They were reminded to re-activate the metronome as needed. There was one report of the suction cup coming off of the device. In this case, the crew quickly reassembled the device and continued adequate ACD-CPR. Importantly, the rescuers were able to continue delivering S-CPR during these incidents.

8.7 Pre-Hospital Care

Study arms were well balanced in terms of the duration of CPR and dose of epinephrine and a proportional number were transported to the hospital, as shown in **Table 8.12**.

Table 8.12 Pre-hospital Care (mITT)

	S-CPR (n=813)	ResQCPR (n=842)	p-value
EMS CPR duration, minutes (mean ± SD)	27.60 ± 12.25	28.12 ± 11.45	0.366
Epinephrine dose, mg (mean ± SD)			
1:1000	3.0 ± 2.0 (n=8)	5.5 ± 1.7 (n=4)	0.060
1:10000	3.6 ± 1.8 (n=743)	3.7 ± 1.8 (n=763)	0.615
Transported to hospital	478 (58.8)	485 (57.6)	0.618

[1]Numbers shown are subjects (%) unless otherwise indicated.

8.8 In-Hospital Care

Subjects admitted to the hospital in both study arms received similar types of care, as shown in **Table 8.13**. Nearly 40% were treated with therapeutic hypothermia in both treatment arms, and nearly 45% were made "do not resuscitate" (DNR) after admission in both treatment arms. More subjects in the ResQCPR group underwent cardiac catheterization, coronary bypass surgery, and survived to hospital discharge, but these differences were not significant. Subjects who were candidates for these procedures were likely to be those who were more hemodynamically stable prior to these procedures. Since hospital personnel were unaware of the method of CPR delivered to study subjects, it is possible that the higher number of ResQCPR subjects recommended for the procedures reflected the better status in those subjects. The average duration of hospital stay was similar between treatment arms, approximately 12 days. Most of the subjects in both groups were discharged to their homes and there were no significant differences in where the subjects went (e.g., home, rehabilitation facility, skilled nursing) after hospital discharge.

Table 8.13 In-Hospital Treatment and Neurologic Outcomes at Hospital Discharge (mITT)[1]

	S-CPR (N=813)	ResQCPR (N=842)	p-value
In-hospital hypothermia (% admitted)	85 (39.4)	93 (38.9)	0.923
Cardiac catheterization (% admitted)	72 (33.3)	100 (41.8)	0.053
coronary stenting (% admitted)	28 (13.0)	38 (15.9)	0.424
Implanted cardiodefibrillator (% admitted)	30 (13.9)	41 (17.2)	0.366
Pacemaker placed (% admitted)	3 (1.4)	2 (0.8)	0.673
Coronary bypass surgery (% admitted)	6 (2.8)	15 (6.3)	0.078
Made DNR after admission (% admitted)	95 (44.0)	109 (45.6)	0.080
Duration hospital stay, days (mean +/- SD, days)	11.8 ± 9.3	12.7 ± 9.1	0.601
Discharge location:			0.200
Home	47	67	
Rehab	8	17	
Long term care/nursing home/other	20	19	
Not available	5	2	

[1]Abbreviations: DNR= do not resuscitate. Data shown are subjects (%) unless indicated otherwise.

8.9 Effectiveness Results

8.9.1 Primary Composite Effectiveness and Safety Endpoint

The primary study endpoint was a composite safety and effectiveness endpoint: survival to hospital discharge with favorable neurologic function (a modified Rankin Score (mRS) ≤3) where this endpoint was to be primarily analyzed in mITT subjects including subjects with a non-traumatic OHCA of presumed cardiac etiology.

The primary study endpoint results are shown in **Table 8.14**. The study results were positive and the primary endpoint was met. The treatment assignment to ResQCPR resulted in significantly more subjects who survived to hospital discharge with favorable neurological function (8.9%) versus those treated only with S-CPR (5.8%) (p=0.019). The odds ratio for this difference was 1.58 with 95% confidence interval boundaries of 1.06 and 2.35. This reflects a greater than 50% increase in the proportion of subjects who survived to hospital discharge with favorable neurological function in the ResQCPR group compared to S-CPR.

These positive results were substantiated further by the significantly greater number of subjects with lower mRS score consistent with better neurological function in the ResQCPR treatment group. More subjects had full or nearly complete restoration of their brain functionality at the time of hospital discharge (p=0.034): a total of 22 subjects with a perfect or near perfect neurological score in the device arm versus 11 in the control arm. These results are consistent with the underlying mechanism of action of the study devices that are designed to significantly augment perfusion of the brain and heart when compared with S-CPR alone. Importantly, the ResQCPR treatment was not associated with proportionally more subjects with poor neurological outcomes at the time of hospital discharge.

Table 8.14 Hospital Discharge with mRS≤3 [Primary Endpoint] (mITT)

	S-CPR (N=813)	**ResQCPR (N=842)**	**p-value**
Hospital discharge with mRS ≤ 3 PRIMARY ENDPOINT	**47 (5.9)**	**75 (8.9)**	**0.019**[1]
mRS at hospital discharge[3]			0.037
mRS 0	3	11	
mRS 1	8	11	
mRS 2	26	30	
mRS 3	10	23	
mRS 4	10	10	
mRS 5	16	18	
mRS 6 (death)	727	735	
Survived, mRS not available	7	2	
Survival outcome data not available	6	2	

[1]Odds ratio 1.58, 95% confidence interval = 1.07, 2.36 (based on subjects with known status)

8.9.2 Analysis of All Subjects Enrolled in the Pivotal Phase (ITT Population)

A supplemental analysis evaluated the primary effectiveness and safety outcome on all randomized subjects (entire ITT population). The ITT population included subjects who had an arrest of non-cardiac etiology and thus were less likely to benefit from CPR efforts.
The ITT analyses for survival to hospital discharge with favorable neurologic function are shown in **Table 8.15**.

Table 8.15 Hospital Discharge with mRS≤3 (ITT)

	S-CPR (N=1201)	ResQCPR (N=1269)	p-value
Hospital discharge with mRS ≤ 3 PRIMARY ENDPOINT	**71 (5.9)**	**101 (8.0)**	**0.057[1]**
mRS at hospital discharge[3]			0.077
mRS 0	7	18	
mRS 1	12	18	
mRS 2	34	36	
mRS 3	18	29	
mRS 4	15	19	
mRS 5	28	28	
mRS 6 (death)	1072	1114	
Survived, mRS not available	9	2	
Survival outcome data not available	6	5	

[1]Odds ratio 1.37, 95% confidence interval = 0.99, 1.90 (based on subjects with known status)

The ITT results were supportive of the primary study endpoint and showed a strong trend in favor of the ResQCPR treatment arm in terms of increased survival to hospital discharge with favorable neurological function (8.0%) versus S-CPR (5.9%) (p=0.057). A total of 36 subjects were discharged with normal or near normal neurological function in the ResQCPR arm versus 19 in the S-CPR arm, consistent with the improved distribution of neurological scores observed for the mITT population. In addition, there was no increase in the number of subjects with poor long-term neurological function between treatment groups.

8.9.3 Per Protocol and Run-in Phase Analyses

The pre-specified *per protocol* analysis was performed for the treatment delivered based upon the randomization schedule. There were a total of 65 subjects excluded from the per protocol analysis in the mITT population. These excluded subjects included 17 subjects with unobtainable primary endpoint outcomes, 10 S-CPR subjects who had investigational devices used, and 43 ResQCPR subjects where protocol deviations were reported indicating that one or both study devices were not used and should have been (data were unobtainable in one subject missing the primary endpoint outcome). In an additional 12 ResQCPR subjects, it was indicated that one or both study devices were not used as all 12 cases had a return of spontaneous circulation (ROSC). The protocol specifically indicated that study devices were to be removed (or not placed to begin with) in the event of a ROSC. Based upon this *per protocol* analysis plan, the survival to hospital discharge with a mRS ≤3 rates for subjects that met criteria for the mITT population (n

= 1655-65=1590) were 5.9% (47/790) for S-CPR treatment and 8.8% (70/800) for ResQCPR treatment (p=0.034).

The run-in phase represented the first time that ResQCPR was used in humans in the U.S. Results from the run-in phase for 197 subjects who met mITT criteria were consistent with the survival advantage observed with ResQCPR treatment in the pivotal trial. More subjects survived to hospital discharge with a mRS≤3 with ResQCPR (9/98 or 9.2%) compared with S-CPR (3/99 or 3.0%) (nominal p-value= 0.082). Although the sample size was too small to observe a statistically significant difference, the odds ratio was greater than 3.

Taken together, these findings strongly support the conclusion that ResQCPR is more effective than S-CPR in improving survival with favorable neurological function after OHCA of presumed cardiac etiology. As shown by the results of the additional analyses below, including the secondary effectiveness and safety endpoint analysis, there was a consistent approximately 3% absolute (50% relative) increase in the number of neurologically sound survivors in the ResQCPR treatment group in the mITT population, regardless of the multiple ways the pivotal study data were analyzed based upon pre-specified and post-hoc sensitivity analyses.

8.9.4 Secondary Effectiveness Endpoint

It was anticipated that full neurological recovery after cardiac arrest could take up to six months in some subjects. Therefore, a pre-specified secondary endpoint that focused on long-term neurological function in the mITT population was proposed. Mean Cognitive Abilities Screening Instrument (CASI) scores for patients receiving ResQCPR were hypothesized to be superior 90 days and 365 days after cardiac arrest when compared with subjects treated with S-CPR. There was a statistically significant 44% increase in survival to 90 days and 49% increase in survival to 365 days after OHCA in the ResQCPR treatment arm compared with S-CPR (p = 0.024 and 0.030, respectively).The pre-specified secondary effectiveness endpoint was an evaluation of long-term neurological function for subjects in the mITT population. Mean 90 and 365 day CASI scores were not significantly different among survivors who were discharged from the hospital (p=0.549 and 0.100, respectively) as hypothesized. These mean scores (**Table 8.16**) included subjects who died after hospital discharge, with a CASI score equal to 0 assigned to those who died. More than 85% of the one year survivors in both study arms completed the one year CASI assessment. The mean ± S.D. CASI scores for these subjects were 93.7 ± 11.8 (n=30) in the S-CPR arm and 94.7 ± 4.4 (n=41) in the ResQCPR arm (p=0.68), consistent with full or nearly full recovery in both groups. There were only three patients with CASI scores <70, a score consistent with poor neurological function, in both groups. These results are important clinically as they indicate that: 1) there were significantly more long-term survivors with ResQCPR treatment, 2) when compared with S-CPR, ResQCPR did not increase the number of long-term survivors with severe neurologic deficits and 3) nearly all survivors in both groups had normal or almost normal cognitive function by one year after OHCA. The CASI scores for the ITT population, as shown in **Table 8.17**, provide further support of the lack of long-term neurological impairment associated with ResQCPR versus S-CPR for all subjects treated, regardless of the etiology of their non-traumatic arrest.

Table 8.16 Secondary Effectiveness Endpoint Results (mITT)

	S-CPR (N=813)	ResQCPR (N=842)	p-value*
Survival to 90 days	58 (7.3%)	87 (10.5%)	0.024
Not available	15	9	
CASI[1] (mean ± SD) at 90 days	69.86 ± 41.68	74.38 ± 37.48	0.549
Survival to 1 year	48 (6.0%)	74 (9.0%)	0.030
Not available	19	20	
CASI (mean ± SD) at 365 days	57.39 ± 47.04	71.89 ± 41.04	0.100

Data expressed as number (%) or mean (SD) unless otherwise stated and include all patients who met final study mITT analysis population criteria

* The p-values for survival to 90 days and 1 year are unadjusted.

[1]Cognitive Abilities Screening Instrument (CASI) assessed attention and short-term memory, long-term memory, judgment, spatial ability, and concentration on a scale of 0-100 in which 100 is a perfect score.

Table 8.17 Secondary Effectiveness Endpoint Results (ITT)

	S-CPR (N=1201)	ResQCPR (N=1269)	p-value*
Survival to 90 days	88 (7.3%)	116 (9.1%)	0.108
Not available	24	24	
CASI[1] (mean ± SD) at 90 days	69.65 ± 41.11	73.28 ± 38.20	0.584
Survival to 1 year	68 (5.7%)	96 (7.6%)	0.062
Not available	30	36	
CASI (mean ± SD) at 365 days	53.42 ± 46.80	62.83 ± 44.52	0.215

Data expressed as number (%) or mean (SD) unless otherwise stated

* The p-values for survival to 90 days and 1 year are unadjusted.

[1]Cognitive Abilities Screening Instrument (CASI) assessed attention and short-term memory, long-term memory, judgment, spatial ability, and concentration on a scale of 0-100 in which 100 is a perfect score.

8.9.5 Additional Pre-Specified Secondary Endpoints

8.9.5.1 Survival Rates from Return of Spontaneous Circulation to One Year for mITT and ITT Subjects

One of the major objectives of the ResQTrial was to determine the safety and effectiveness of the ResQCPR treatment from the time of a return of spontaneous circulation (ROSC) to survival status one year later. The survival outcomes for mITT subjects from ROSC to one year later are shown in **Table 8.18**. Proportional differences between the two treatment groups were observed to become larger over time. Approximately 50% more subjects treated with ResQCPR were alive one year after OHCA compared with those treated with S-CPR. This difference had a nominal unadjusted p=0.030.

Table 8.18 Survival from ROSC to One Year (mITT)[1]

	S-CPR (n=813)	ResQCPR (n=842)	p-value
ROSC during CPR before hospital admission	324 (39.9)	345 (41.0)	0.689
Admitted to hospital	216 (26.6)	239 (28.4)	0.474
Survived to 24 hours following arrest Not available	176 (21.6) 9	199 (23.6) 6	0.410
Survival to hospital discharge Not alive at hospital discharge Not available	80 (9.9) 727 6	105 (12.5) 735 2	0.118
Alive at 30 days Not alive at 30 days Not available	65 (8.1) 738 10	96 (11.5) 741 5	0.025
Alive at 90 days Not alive at 90 days Not available	58 (7.3) 740 15	87 (10.4) 746 9	0.029
Alive at 1 year Not alive at 1 year Not available	48 (6.0) 746 19	74 (9.0) 748 20	0.030

[1]Numbers shown are subjects (%) unless otherwise indicated.

Analysis of survival rates of all 2470 subjects in the ITT population demonstrated a similar long-term benefit of ResQCPR treatment (**Table 8.19**). There was a strong trend towards increased one year survival in the overall ITT population with ResQCPR treatment versus S-CPR alone.

Table 8.19 Survival from ROSC to One Year (ITT)[1]

	S-CPR (n=1201)	ResQCPR (n=1269)	p-value
ROSC during CPR before hospital admission	490 (40.8)	524 (41.3)	0.806
Admitted to hospital	342 (28.5)	381 (30.0)	0.401
Survived to 24 hours following arrest Not available	277 (23.1) 12	310 (24.4) 11	0.701
Alive at hospital discharge Not alive at hospital discharge Not available	123 (10.2) 1072 6	150 (11.8) 1114 5	0.428
Alive at 30 days Not alive at 30 days Not available	98 (8.2) 1086 17	131 (10.3) 1123 15	0.071
Alive at 90 days Not alive at 90 days Not available	88 (7.3) 1089 24	116 (9.1) 1129 24	0.108
Alive at 1 year Not alive at 1 year Not available	68 (5.7) 1103 30	96 (7.6) 1137 36	0.062

[1]Numbers shown are subjects (%) unless otherwise indicated.

8.9.5.2 Secondary Endpoints Based Upon Long-Term Neurological Recovery

A comprehensive series of pre-specified neurological tests were performed to assess long-term neurological function and recovery in all survivors after OHCA.

Results from the Cerebral Performance Category (CPC), Overall Performance Category (OPC), Beck Depression Inventory (BDI), Cognitive Abilities Screening Instrument (CASI), Health Utilities Index Mark 3 (HUI3), Trail Making Tests (Parts A and B), Quality of Life Survey, and Disability Rating Scale (DRS) each showed that subjects in both treatment groups who survived for at least 90 days had a return to normal or near neurological function and thereafter up to one year. A summary of the results from these neurological assessments comparing outcomes between the two treatment groups one year after cardiac arrest for the mITT population and the entire ITT population, are shown in **Table 8.20** and **Table 8.21**.

Table 8.20 Neurologic Assessments One Year (mITT)

	S-CPR (n=813)	**ResQCPR (n=842)**	**p-value**
CPC ≤ 2 at one year	43(5.4)	62 (7.6)	0.086
OPC ≤2 at one year	42 (5.3)	52 (6.3)	0.395
Beck Depression Inventory (mean score ± SD)	5.23 ± 6.29 (n=35)	5.46 ± 5.93 (n=57)	0.862
CASI (mean score ± SD, among survivors)	93.73 ± 11.77 (n=30)	94.68 ± 4.40 (n=41)	0.676
HUI 3 (mean score ± SD)	12.49 ± 4.45 (n=37)	12.10 ± 6.00 (n=60)	0.736
Trail making A (mean score ± SD)	49.56 ± 43.37 (n=32)	47.10 ± 27.26 (n=39)	0.772
Trail making score B (mean score ± SD)	87.48 ± 43.12 (n=27)	100.54 ± 64.47 (n=35)	0.368
Quality of Life (mean score ± SD)	2.02 ± 0.79 (n=41)	2.09 ± 0.99 (n=64)	0.706
DRS[4] (mean score ± SD)	1.39 ± 3.12 (n=41)	2.19 ± 5.68 (n=63)	0.412

[1]Abbreviations: ICD= Implanted cardiodefibrillator; CPC= Cerebral performance category; OPC=Overall performance category; CASI= Cognitive Abilities Screening Instrument; HUI= Health Utilities Index Mark 3; DRS= Disabilities Rating Score; averages for Beck, CASI, HUI3, and DRS include complete assessments only
[2]Mann Whitney comparison of CPC and OPC by group (based on known responses)
[3]Secondary endpoint-long term neurologic function, evaluated according to a hierarchical closed test procedure with imputed CASI score of 0 for subjects who died after discharge and prior to 365 days.
[4]DRS- 9 categories defined as follows: None (score of 0), Mild (score of 1), Partial (score of 2-3), Moderate (score of 4-6), Moderately severe (score of 7-11), Severe (score of 12-16), Extremely severe (score of 17-21), Vegetative state (score of 22-24), and Extreme vegetative state (score of 25-29)

Table 8.21 Neurologic Assessments One Year After Cardiac Arrest (ITT)

	S-CPR (n=1201)	ResQCPR (n=1269)	p-value
CPC $\leq$ 2 at one year	56 (4.8)	76 (6.2)	0.129
OPC $\leq$2 at one year	54 (4.6)	73 (6.0)	0.145
Beck Depression Inventory (mean score ± SD)	6.52 ± 7.25 (n=48)	5.87 ± 6.04 (n=69)	0.599
CASI (mean score ± SD, among survivors)	91.93 ± 13.47 (n=43)	92.33 ± 12.33 (n=49)	0.883
HUI 3 (mean score ± SD)	13.85 ± 7.34 (n=52)	12.45 ± 5.87 (n=73)	0.241
Trail making A (mean score ± SD)	48.95 ± 41.69 (n=43)	50.96 ± 32.54 (n=47)	0.799
Trail making score B (mean score ± SD)	85.75 ± 38.87 (n=36)	111.79 ± 75.23 (n=42)	0.055
Quality of Life (mean score ± SD)	2.05 ± 0.98 (n=56)	2.20 ± 1.06 (n=79)	0.407
DRS[4] (mean score ± SD)	2.46 ± 5.47 (n=57)	2.91 ± 6.09 (n=79)	0.654

[1]Abbreviations: ICD= Implanted cardiodefibrillator; CPC= Cerebral performance category; OPC=Overall performance category; CASI= Cognitive Abilities Screening Instrument; HUI= Health Utilities Index Mark 3; DRS= Disabilities Rating Score; averages for Beck, CASI, HUI3, and DRS include complete assessments only
[2]Mann Whitney comparison of CPC and OPC by group (based on known responses)
[3]Secondary endpoint-long term neurologic function, evaluated according to a hierarchical closed test procedure with imputed CASI score of 0 for subjects who died after discharge and prior to 365 days.
[4]DRS- 9 categories defined as follows: None (score of 0), Mild (score of 1), Partial (score of 2-3), Moderate (score of 4-6), Moderately severe (score of 7-11), Severe (score of 12-16), Extremely severe (score of 17-21), Vegetative state (score of 22-24), and Extreme vegetative state (score of 25-29)

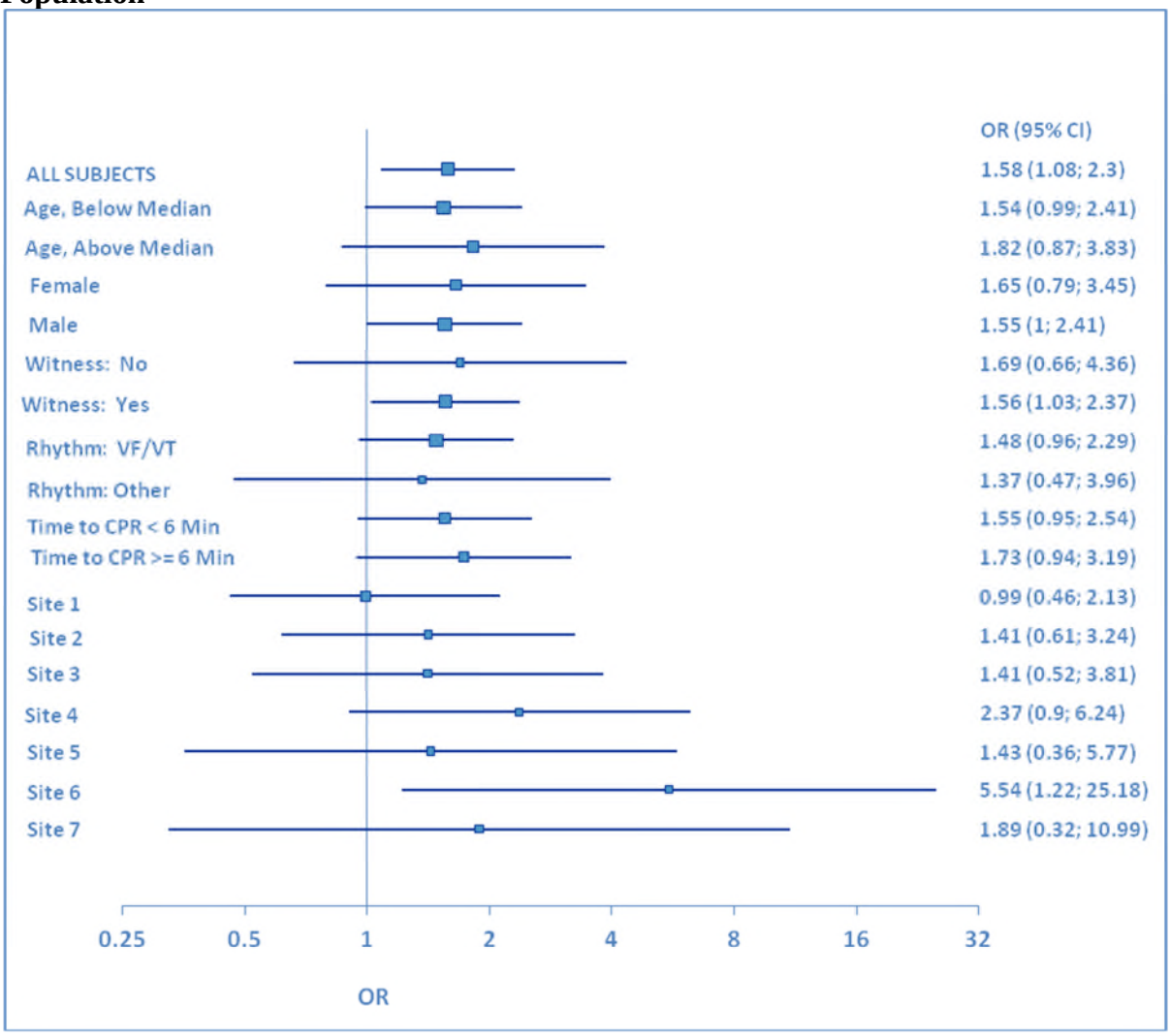
These evaluations of cognitive, function, and emotional functionality demonstrated that >95% of all subjects in both treatment arms who survived 90 and 365 after OHCA had normal or nearly normal neurological function. An assessment of the subjects' quality of life one year after OHCA also demonstrated that >95% of survivors in both treatment groups had a full or nearly full restoration of their quality of life compared with pre-arrest perceptions. **Section 12, Appendix 2** provides additional outcome data for each of these respective tests at the multiple time points between hospital discharge up to one year after OHCA. In the aggregate, this comprehensive neuropsychological battery of tests demonstrated that treatment with ResQCPR did not increase the number of neurologically impaired subjects long-term. Moreover, the vast majority of the subjects treated with ResQCPR who survived long-term had excellent neurologic function.

8.9.5.3 Subgroup Analyses

The rates of hospital discharge with a mRS$\leq$3 were examined by pre-specified subgroup analyses based upon age, gender, time from 911 to CPR, witnessed/unwitnessed status of the cardiac arrest, and first recorded rhythm. As shown in the Forest Plots in **Figure 8.4**, the positive primary endpoint results with ResQCPR treatment were consistent across all of these subgroups. Although not pre-specified, there was also a consistent ResQCPR benefit between study sites. In some of these analyses, such as the subgroup of subjects with a witnessed arrest and those who

were male, ResQCPR treated subjects had a statistically higher likelihood of survival to hospital discharge with favorable neurological status. A study site poolability analysis showed no evidence of a difference in odds ratio between sites (Homogeneity of Odds Ratio Test, p= 0.510). The Common Mantel-Haenszel Odds Ratio Estimate across Sites was 1.630, with a 95% confidence interval of 1.122, 2.389.

Figure 8.4 Effect of Age, Gender, Witnessed Status, Initial Recorded Rhythm and Study Site, on Estimated Odds Ratio (OR) for Primary Endpoint (ResQCPR vs. s-CPR) in mITT Population



Time to CPR treatment is well known to impact survivability. In order to estimate the interval from collapse to start of CPR, the arrest needed to be witnessed. As shown in **Table 8.22**, when an arrest was witnessed or ResQCPR was started within 10 minutes from the receipt of the 911 call, more subjects survived with favorable neurological function in the ResQCPR group. The nominal unadjusted p-values for these pre-specified exploratory subgroups are also shown. These observations are consistent with the importance of applying the devices as soon as possible after

cardiac arrest in order to have a clinically significant benefit during the circulatory phase of cardiac arrest.[103]

Table 8.22 mRS Results at Hospital Discharge by Witness Status and Time from Collapse to CPR Start <10 Minutes (mITT)

	s-CPR	ResQCPR	Total	p-value[1]
Subjects with witnessed arrest	**459**	**480**	**939**	
mRS:				
0	3	11	14	
1	7	9	16	
2	20	23	43	
3	10	20	30	
4	7	10	17	
5	10	13	23	
6	391	391	782	
Survival at discharge not available	5	1	6	
Survived, mRS not available	6	2	8	
Hospital discharge with mRS ≤ 3 (Primary Endpoint)	40	63	103	0.046
Subjects with witnessed arrest and collapse to CPR start < 10 minutes[1]	372	402	774	
mRS:				
0	2	10	12	
1	5	8	13	
2	19	22	41	
3	10	20	30	
4	7	10	17	
5	9	12	21	
6	309	318	627	
Survival at discharge not available	5	0	5	
Survived, mRS not available	6	2	8	
Hospital discharge with mRS ≤ 3 (Primary Endpoint)	36	60	96	0.038
Subjects with witnessed arrest and collapse to CPR start ≥ 10 minutes	82	76	158	
mRS:				
0	1	1	2	
1	2	1	3	
2	1	0	1	
3	-	-	-	
4	-	-	-	
5	1	1	2	
6	77	72	149	
Survival at discharge not available	0	1	1	
Hospital discharge with mRS ≤ 3 (Primary Endpoint)	4	2	6	0.683

[1]These numbers represent nominal unadjusted p-values for these pre-specified exploratory subgroups

Similar to other OHCA studies, subjects with a first recorded rhythm of ventricular fibrillation (VF) had the greatest likelihood of survival.[9] The relative distribution between the ResQCPR and S-CPR groups for VF, pulseless electrical activity (PEA) and asystole as the first recorded rhythm was similar between treatment groups (**Table 8.23**). However, there was a 50% increase

in the absolute number of subjects in the mITT analysis population with VF/VT as the first recorded rhythm who survived to hospital discharge with a mRS ≤3 in the ResQCPR treatment arm versus the S-CPR arm. Far fewer survivors in either group of subjects meeting mITT analysis criteria had an initial rhythm of asystole or PEA.

Table 8.23 Initial Recorded Arrest Rhythm in Subjects with mRS≤3 at Hospital Discharge (mITT)1

Initial recorded rhythm	S-CPR (n=47)	ResQCPR (n=75)	p-value[2]
Ventricular fibrillation and pulseless ventricular tachycardia	40 (85.1)	66 (88.0)	0.813
Asystole	3 (6.4)	6 (8.0)	
Pulseless electrical activity	3 (6.4)	2 (2.7)	
Not available	1 (2.1)	1 (1.3)	

[1]numbers in parentheses are the percentage of survivors with mRS≤3 at Hospital Discharge
[2] The p-value shown is nominal, unadjusted, and calculated for exploratory analysis of the comparison in distributions of first recorded rhythms in the two study groups.

A similar analysis with similar findings is shown in **Table 8.24** for all subjects in the ITT population.

Table 8.24 Initial Recorded Arrest Rhythm in Subjects with mRS≤3 at Hospital Discharge (ITT)[1]

Initial recorded rhythm	S-CPR (n=71)	ResQCPR (n=101)	p-value[2]
Ventricular fibrillation and pulseless ventricular tachycardia	50 (70.4)	71 (70.3)	0.93
Asystole	8 (11.3)	9 (8.9)	
Pulseless electrical activity	10 (14.1)	14 (13.9)	
Not available	3 (4.2)	7 (6.9)	

[1]numbers shown are subjects (%)
[2] The p-value shown is nominal, unadjusted, and calculated for exploratory analysis of the comparison in distributions of first recorded rhythms in the two study groups.

8.9.6 Summary of Pre-specified Safety and Effectiveness Endpoints

Similar to the primary study endpoint results, each of the pre-specified secondary safety and effectiveness endpoints demonstrated a consistently strong trend towards or a significant increase in survival with ResQCPR treatment versus with S-CPR. A survival advantage associated with favorable neurological function was observed for up to one year with ResQCPR treatment in the mITT population. A similar ResQCPR advantage was found in subjects 1) who met mITT analysis criteria and had a witnessed arrest, 2) who had CPR initiated <10 minutes from the time of collapse or 911 call, and 3) regardless of subjects' age and gender or clinical site of the OHCA. Nearly all the survivors treated with ResQCPR had a complete or nearly complete restoration of neurological function within 90 days of the cardiac arrest. Additionally, there was not an increase in the number of subjects with significant neurological impairment when compared with S-CPR. These results demonstrate the consistency of the benefits of ResQCPR when compared with S-CPR in multiple subject subgroups. The combination of the positive results for the pre-specified primary endpoint in the mITT and ITT analysis populations and

these secondary pre-specified short and longer-term endpoints provide strong support for the superiority of ResQCPR when compared with S-CPR for the treatment of non-traumatic OHCA.

8.9.7 Additional Outcome Analyses

To better understand the potential broader implications of the ResQTrial study results and some of its limitations, further analyses were performed after the study was completed. In addition, the Company performed several analyses at FDA's request to help clarify issues related to the implications of stopping the study earlier than planned following the pre-specified interim analysis and the challenges associated with performing resuscitation research under the exception from informed consent for emergency research under 21 CFR § 50.24.

8.9.7.1 Use of ResQCPR in All Non-traumatic Arrest Subjects Enrolled in the ResQTrial Run-in and Pivotal Phases

A total of 2,738 subjects were randomized to ResQCPR or S-CPR during the entire ResQTrial, including the run-in phase, regardless of the etiology of the non-traumatic cardiac arrest. The neurological status at the time of hospital discharge was known in 2,714 of these subjects. For those subjects in the overall ITT population, 7.9% (110/1396) of those randomized to ResQCPR treatment survived to hospital discharge with an mRS ≤3 versus 5.7% (75/1318) of those randomized to S-CPR. The nominal, unadjusted p-value was 0.027. For mITT subjects in the combined run-in and pivotal phases, 9.0% (84/936) who were randomized to ResQCPR treatment survived to hospital discharge with a mRS ≤3 versus 5.6% (50/899) who received S-CPR. The nominal, unadjusted p-value was 0.005. These results were recently published by the study investigators and are similar to those which were observed in the pivotal study for the primary study endpoint.[104]

8.9.7.2 Survival from the Time of Hospital Discharge to One Year

Although the primary study outcome focused on those subjects who survived to hospital discharge with favorable neurological function with an OHCA of presumed cardiac etiology, the one year survival rates for all enrolled subjects known to have survived to hospital discharge as well as those who met mITT analysis criteria were of interest in determining the long-term effectiveness of the study intervention. Using all available study database information, including use of public death records, these analyses provided further insight into the outcomes of nearly all of the subjects in the ResQTrial who were discharged alive from the hospital. As shown in the two Kaplan Meier curves below, one for all subjects in the ITT population and the second from those who met mITT analysis criteria, more subjects survived to one year after hospital discharge when treated with ResQCPR versus S-CPR alone. The nominal p-values for these Kaplan Meier ITT and mITT analysis curves were 0.033 and 0.04, respectively. These findings support the conclusion that the method of CPR delivered by first responders can positively affect the likelihood of long term survival for subjects discharged alive from the hospital following a non-traumatic OHCA. This long-term survival advantage from the time of hospital discharge to one year later demonstrated in the ResQCPR treatment group was observed in the subjects that met mITT analysis criteria and the full ITT populations.

Figure 8.5 Kaplan Meier Survival, All Subjects Discharged Alive (Subjects Who Met Criteria for mITT Analysis)

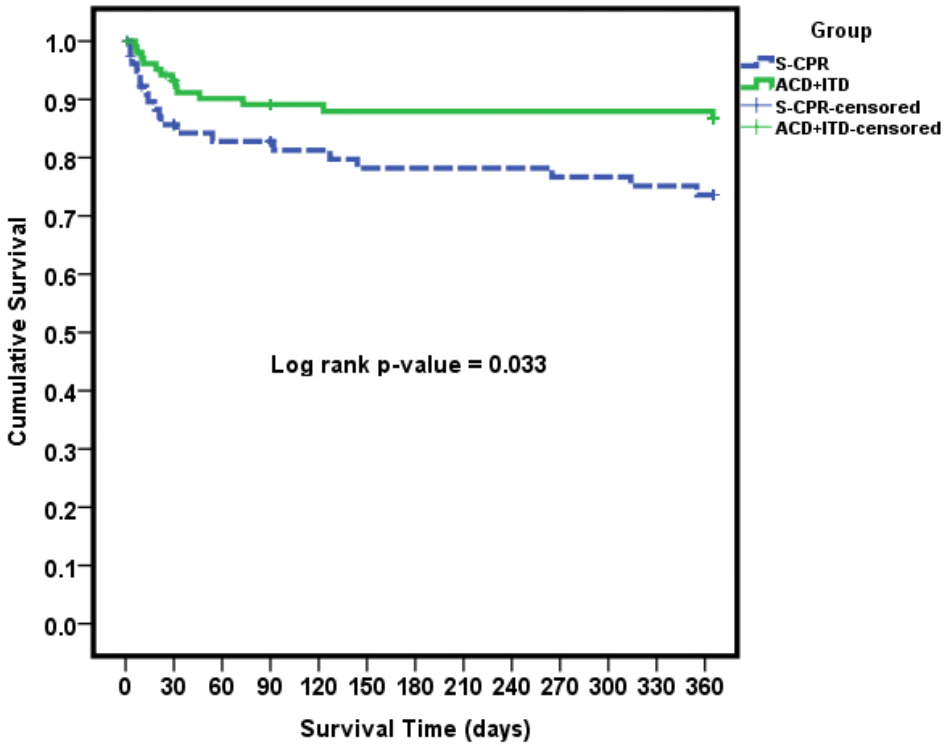
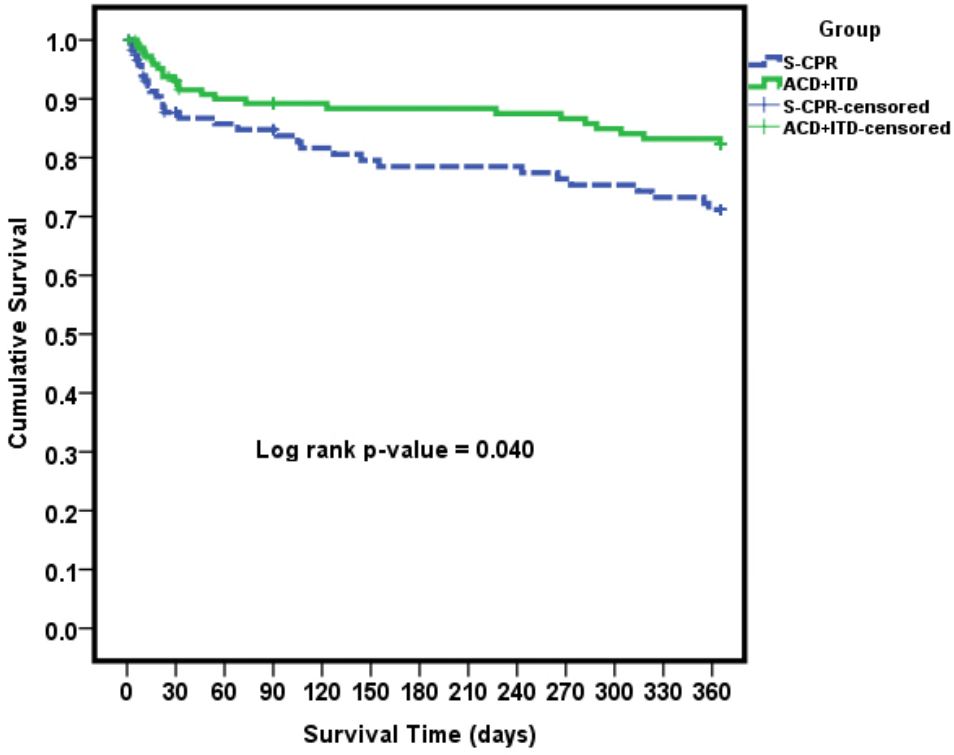


Figure 8.6 Kaplan Meier Survival, All Subjects Discharged Alive (ITT)

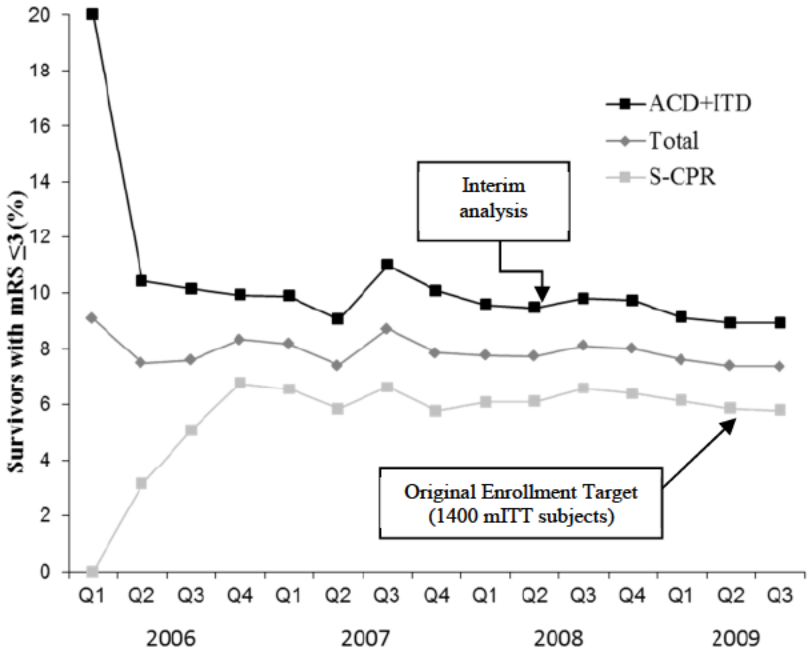


8.9.7.3 Implications of Early Study Termination

At the FDA's request the Company performed an exploratory analysis to assess what the study results would have been if study enrollment was limited to the first 1,400 subjects who met criteria for the mITT analysis.

As shown in **Figure 8.7**, achievement of the primary endpoint of hospital discharge with mRS≤3 stabilized to relatively consistent values in the two study groups over the 45-month period of subject enrollment.

Figure 8.7 Cumulative Rate of Achievement of Primary Endpoint (mITT)



ACD+ITD enrollment (cumulative)	5	174	389	715	842
S-CPR enrollment (cumulative)	6	168	395	703	813
Total enrollment (cumulative)	11	342	784	1418	1655

Figure 8.7 legend: Results are shown by year quarter (Q). Consistent results in both groups were observed throughout the study. Enrollment was initiated in the fourth quarter of 2007 at site 06, and the first quarter of 2009 at site 07. mRS- modified Rankin Scale score; CPR= cardiopulmonary resuscitation

The first 1,400 mITT subjects for this post hoc analysis were selected based on cases sorted by incident date of the out-of-hospital cardiac arrest and ascending case report number. This cohort corresponded to incident dates occurring on or before March 24, 2009, as shown in **Figure 8.7**. Twelve (12) subjects ultimately had unobtainable mRS evaluations in this mITT cohort. A summary of these analyses of the original planned study cohort of 1,400 subjects who met mITT analysis criteria as well as those in the entire ITT population is shown in **Table 8.25** below. Based upon these exploratory analyses, the primary study endpoint would have been achieved had enrollment been limited to the first 1,400 subjects who met criteria for the mITT analysis. As is also shown below, in March 2009 there would have also been a statistically significant survival to hospital discharge with mRS ≤3 advantage for the entire ITT population.

Table 8.25 Summary of Analyses of the Primary Study Endpoint of the Original Planned Study Cohort of 1400 mITT Subjects

Study Population	Primary Endpoint: mRS≤3		p-value[1]
	S-CPR	ResQCPR	
mITT	6.0% (41/684)	9.1% (64/704)	p = 0.033
ITT	5.9% (58/991)	8.2% (85/1033)	p = 0.038

[1]The p-values shown are nominal, unadjusted, and calculated for exploratory analysis purposes

These positive findings provide further support for the robustness of the original study results.

8.9.7.4 Sensitivity Analyses Regarding Unobtainable Primary Endpoint Data

There were 17 subjects with unobtainable mRS values in the primary analysis population (1.0% of the total pivotal mITT population of 1655). In 16 of the 17 cases, mRS could not be determined because the subject had declined to provide informed consent. The remaining subject's mRS could not be determined because they were transferred to a non-participating hospital and medical records could not be obtained.

There were more subjects with unobtainable mRS score without consent in the S-CPR group. Of all subjects (both study groups) for whom consent was provided, 35.0% (112/320) survived to discharge with mRS ≤3. Of all subjects (both study groups) for whom consent was refused, only 4.1% (3/74) survived to discharge with mRS ≤3. Subjects with poor health status (mRS ≥4) were much less likely to provide informed consent, regardless of treatment assignment. Subjects who were transported and admitted to the hospital had, on average, a better mRS status at discharge in the ResQCPR group than in the S-CPR group, and this better status is believed to have influenced the likelihood of obtaining informed consent.

The known information about these 17 subjects in shown in **Table 8.26** below.

Table 8.26 Cases with Unobtainable Survival or mRS Outcomes at Hospital Discharge (mITT, includes all Subjects Transported to Hospital)

	Case Number	Group	Age	Gender	Admitted to Hospital	Survival to 24 hours	Discharged from the hospital	Consent obtained	Primary Endpoint Information (survival to discharge, mRS)	Survival status, study duration (includes public records search)
1	(b)(6)	s-CPR	48	male	Yes	Yes	Yes	No	Survived but mRS n/a	Alive at 1 yr
2		s-CPR	83	female	Yes	Yes	Yes	No	Survived but mRS n/a	Died, < 1 yr
3		RQCPR	50	male	Yes	Yes	Yes	No	Survived but mRS n/a	Alive at 1 yr
4		s-CPR	74	female	Yes	Unknown	Unknown	No	Survival status at Discharge n/a	-
5		RQCPR	47	female	Yes	Yes	Yes	No	Survived but mRS n/a	-
6		s-CPR	62	female	Yes	Unknown	Unknown	No	Survival status at Discharge n/a	-
7		s-CPR	70	male	Yes	Yes	Yes	Yes	Survived but mRS n/a	Alive at 1 yr
8		s-CPR	44	male	Yes	Yes	Yes	No	Survived, mRS n/a	-
9		s-CPR	69	male	Yes	Yes	Yes	No	Survived, mRS n/a	Died, < 90 days
10		s-CPR	46	male	Yes	Yes	Yes	No	Survived, mRS Not Available	-
11		RQCPR	97	female	Unknown	Unknown	Unknown	No	Survival at Discharge n/a	-
12		s-CPR	60	male	Yes	Unknown	Unknown	No	Survival at Discharge n/a	-
13		s-CPR	52	female	Yes	Yes	Unknown	No	Survival at Discharge n/a	Died 12 days post-arrest
14		RQCPR	63	male	Yes	Yes	Unknown	No	Survival at Discharge n/a	Died 6 days post-arrest
15		s-CPR	44	male	Yes	Yes	Yes	No	Survived, mRS n/a	Alive at 30 days, unknown thereafter
16		s-CPR	87	male	Yes	Yes	Unknown	No	Survival at Discharge n/a	-
17		s-CPR	58	male	Yes	Yes	Unknown	No	Survival at Discharge n/a	Died, 2 days post-arrest

Additional sensitivity analyses were performed to better understand the potential implications of the unobtainable outcomes to the overall results. When values were imputed using the observed mRS results by study group in subjects who were admitted to the hospital, then the success rate was estimated to be 9.0% in the ResQCPR group vs. 6.2% in the S-CPR group (p = 0.033). Outcomes for these 17 subjects were also imputed based upon study variables that were potentially predictive of the subjects' condition as assessed with the mRS score. These variables included gender, witnessed status, informed consent status, VF / VT as first recorded rhythm, time from 911 call to start of CPR, and age. When values for the 17 subjects were imputed using a binary logistic regression prediction model based on these study variables, then the success rate was estimated to be 8.9% in the ResQCPR group vs. 5.9% in the S-CPR group (p=0.024).

In addition, a tipping point analysis demonstrated that a loss of statistical significance for the comparison of the primary endpoint between study groups would occur if 5 subjects without endpoint success were removed from the ResQCPR group (p=0.055) (at this tipping point, there would be 23 more subjects who survived with favorable neurologic outcome and a 42% relative increase in survival with good neurologic function in the ResQCPR group).

8.9.7.5 Late Determination of mRS Scores and Inclusion Criteria

Following issuance of the 2008 FDA Guidance document discussed above in **Section 7.5**, the investigators re-petitioned IRBs for permission to examine medical records of those subjects for whom consent could not be obtained or up to the point in time consent was denied. As a result, the mRS status for 46 ITT subjects and 29 mITT subjects with previously unobtainable mRS data, who had neither declined nor gave informed consent, was determined. In cases where cardiac arrest occurred prior to the publication of the October 2008 guidance, there was a long delay between the time of the arrest and when the site investigators received permission from the IRBs to review the subjects' medical records. To determine the impact of these cases on the study results, these 29 subjects were removed from the mITT population. The resulting success rates for the primary endpoint were estimated to be 8.8% in the ResQCPR group vs. 5.7% in the S-CPR group (p = 0.021).

An additional 17 cases were identified where IRB approval for medical review was sought and obtained on an ad hoc basis after hospital discharge for subjects who neither provided nor declined informed consent. These 17 cases, wherein mRS scores at hospital discharge were determined by review of the medical record after IRB approval, were added to the 29 cases referenced above and these 46 subjects were removed from the mITT population. The resulting success rates for the primary endpoint were estimated to be 8.7% in the ResQCPR group vs. 5.7% in the S-CPR group (p = 0.020).

In addition to publication of the 2008 FDA Guidance document, based upon the data quality assurance processes there were several other reasons why there may have been a change in a subject's mRS score or exclusion from the mITT population during the course of the study. A total of 28 subjects were removed from the mITT population (but remained in the ITT population) based on a CEC review that, because of delays in obtaining relevant information, occurred late relative to their cardiac arrest date. These subjects were added back to the original mITT population for the purpose of this analysis. The resulting success rates for the primary

endpoint were estimated to be 8.8% in the ResQCPR group vs. 6.2% in the S-CPR group (p = 0.051).

In conclusion, when subjects with delayed determination of mRS, either through application of the 2008 FDA Guidance document or IRB requests for medical record reviews, were removed from the mITT population, the proportion of subjects with mRS≤3 in the ResQCPR group exceeded that in the S-CPR group in the mITT population (related nominal p-values of 0.021 and 0.020). When 28 cases with delayed CEC adjudication of removal from the mITT were added back to the mITT population, the proportion of ResQCPR subjects with mRS≤3 (8.8%) exceeded that for S-CPR subjects (6.2%) with a nominal p-value of 0.051.

8.9.7.6 Summary Table of Additional Analyses

Additional analyses were performed that were not pre-specified but based upon requests for clarification by FDA. In addition, several sensitivity analyses were performed to further assess the safety and effectiveness of ResQCPR. The findings from these further analyses are summarized in **Table 8.27** together with the main pre-specified primary endpoint analyses**.** Together these analyses demonstrate a consistent benefit of the ResQCPR treatment, ranging from 19.4% to 60.7%, regardless of the analysis population, subpopulation, or assumptions made in the analyses. The nominal unadjusted p-values associated with those analyses in this table demonstrate the robustness of the original finding of a significant difference for the primary study endpoint between study groups in the mITT population. Additional post-hoc analyses performed by the FDA, which show similar consistent benefit of the ResQCPR treatment, are included in **Section 13 Appendix 3**.

Table 8.27 Summary of Primary Endpoint Outcome by Analysis Population (ITT, mITT)

Analysis population/subgroup	**Primary Endpoint: Survival to Hospital discharge with mRS≤3**		**Results**	**Relative % increase from S-CPR to ResQCPR**
	S-CPR	**ResQCPR**		
Run-In + Pivotal ITT	5.7% (75/1318) Missing: 1.3% (17)	7.9% (110/1396) Missing: 0.5% (7)	p = 0.027	38.6%
Run-In + Pivotal mITT	5.6% (50/899) Missing: 1.4% (13)	9.0% (84/936) Missing: 0.4% (4)	p = 0.005	60.7%
Pivotal ITT	6.0% (71/1186) Missing: 1.2% (15)	8.0% (101/1262) Missing: 0.6% (7)	p = 0.057	33.3%
Pivotal mITT	5.9% (47/800) Missing: 1.6% (13)	8.9% (75/838) Missing: 0.5% (4)	p = 0.019	50.8%
Original Planned Study Enrollment of 1400 Subjects	6.0% (41/684) Missing: 1.3% (9)	8.9% (64/704) Missing: 0.4% (3)	p = 0.033	48.3%
Cui-Hung-Wang Method (to	Z_{CHW} Statistic = 2.18, p = 0.029			

Analysis population/subgroup	Primary Endpoint: Survival to Hospital discharge with mRS≤3		Results	Relative % increase from S-CPR to ResQCPR
	S-CPR	ResQCPR		
maintain alpha level when sample size is increased)				
Bootstrap Pivotal mITT	Odds ratio = 1.58, 95% Confidence Interval (1.08, 2.30)			
Imputation of 17 unobtainable mRS scores predicted from known study group mRS results in subjects admitted to hospital	6.2% (50/813) Missing: 0	9.0% (76/842) Missing: 0	p = 0.033	45.2%
Imputation of 17 unobtainable mRS scores based on predictions from covariates	5.9% (48/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.024	50.8%
Worst case assumption for unobtainable mRS scores of mRS≥4 in both study groups	5.8% (47/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.018	53.4%
Worst case assumption for unobtainable MRS scores of mRS≥4 for ResQCPR and best assumption of mRS≤3 for S-CPR	7.4% (60/813) Missing: 0	8.9% (75/842) Missing: 0	p = 0.281	20.3%
Per Protocol	5.9% (47/790)	8.8% (70/800)	p = 0.034	49.2%
Addition of 192 ITT cases of drug overdose / metabolic imbalance to mITT	6.6% (58/877)	9.0% (86/952)	p = 0.056	36.4%
Addition of 163 ITT cases of medication/drug overdose to mITT	6.6% (57/865)	9.0% (84/935)	p = 0.065	36.4%
Removal of 29 mITT cases where 2008 FDA Guidance document applied to obtain mRS	5.7% (45/787)	8.8% (72/822)	p = 0.021	54.4%
Removal of 46 mITT cases where FDA Guidance applied or IRB permission to obtain mRS	5.7% (44/778)	8.7% (71/814)	p = 0.020	52.6%

Analysis population/subgroup	Primary Endpoint: Survival to Hospital discharge with mRS≤3		Results	Relative % increase from S-CPR to ResQCPR
	S-CPR	ResQCPR		
Addition of 28 ITT cases with delayed CEC adjudication to mITT	6.2% (50/806)	8.8% (76/860)	p = 0.051	41.9%
Treatment Delivered: S-CPR subjects with 0 devices used ResQCPR with ≥ 1 device used	5.9% (47/790) Missing: 13	8.3% (67/811) Missing: 3	p = 0.080	40.7%
Treatment Delivered: S-CPR with 0 devices used ResQCPR with 2 devices used	5.9% (47/790) Missing: 13	8.1% (63/779) Missing: 3	p = 0.113	37.3%
Treatment Delivered: Subjects with 0 devices used Subjects with 2 devices used	6.7% (55/817)	8.0% (63/784)	p = 0.339	19.4%
Kaplan-Meier: Survival through 1 Year for Subjects Discharged Alive (mITT)	0.736 at 1 Year	0.868 at 1 Year	p = 0.033	
Kaplan-Meier: Survival through 1 Year for Subjects Discharged Alive (ITT)	0.712 at 1 Year	0.823 at 1 Year	p = 0.040	

As shown in **Table 8.27** a Cui-Hung-Wang (CHW) analysis was performed to examine an alternative method of determining the statistical significance of primary endpoint results in the mITT population. The CHW approach is taken to ensure that the alpha error level is maintained when the sample size is adaptively increased. Since the CHW method down-weights the contribution of subject data that are collected after an adaptive adjustment, it results in an alpha cost to the significance level of study results. The difference between the ResQCPR and S-CPR remain statistically significant with a p-value of 0.029 with the CHW approach. To further assess the robustness of the relative success rates in the two study groups in the mITT population, a bootstrapping analysis simulating 1000 trials was used to estimate the odds ratio associated with ResQCPR vs. S-CPR. Each simulated trial represents a mITT population of 1,655 subjects created by sampling with replacement from the original mITT cohort.

Also shown in **Table 8.27** is a post-hoc 'treatment-method delivered' analysis that compared all subjects in the mITT population who were randomized to the ResQCPR group where one or both devices were documented to have been used with the S-CPR group who had no devices used. One analysis entitled *Treatment Delivered: Subjects with 0 devices used, Subjects with 2 devices used* is unlikely to reflect a valid assessment of the safety and effectiveness of ResQCPR in that it did not to take into account the fact that S-CPR was first started on most patients in the device

arm of the study as the ResQCPR study devices were being removed from the study bags and prepared for use.

It should also be noted that FDA performed a post-hoc evaluation of all study results using an alpha level of 0.022 instead of the FDA-approved alpha level of 0.049. The FDA states that this post-hoc use of an 0.022 alpha level partially addresses concerns the FDA has about possible alpha inflation occurring as a result of the periodic DSMB reviews of the blinded study results, the planned interim analysis, and potential unblinding of the Company during the study.
The study protocol did not allow for the DSMB to terminate the study early as a result of the data summaries prepared for DSMB review or at the time of the, interim analysis. Further, the Company maintains that it was not unblinded to aggregate data during the study. There cannot be an inflation of the Type I error if there is no opportunity to reject the hypothesis associated with the primary study endpoint.

8.9.7.7 In-Hospital Therapeutic Hypothermia

The relationship of post-resuscitation, in-hospital therapeutic hypothermia (TH) with achievement of the primary endpoint was evaluated. As shown in **Table 8.28** in the absence of TH, there were proportionally more patients in the ResQCPR group who achieved the primary endpoint, as compared with the S-CPR group: 29.4 % versus 17.6% (nominal unadjusted p-value =0.03).

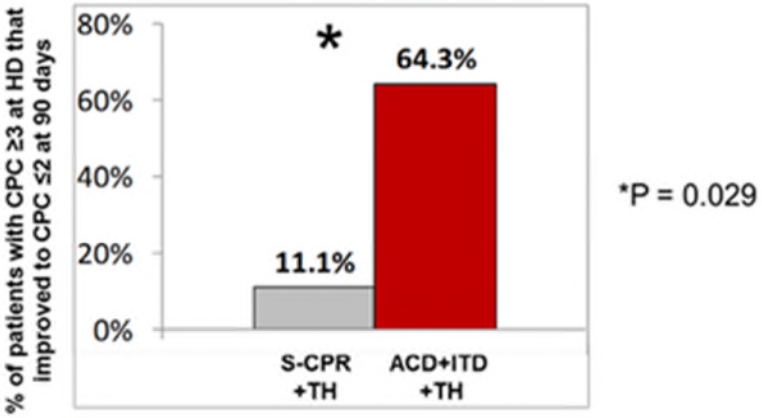
Table 8.28 Association Between Primary Endpoint and Use of Post-resuscitation In-hospital Therapeutic Hypothermia (mITT)

	mRS ≤3	mRS ≥4	p-value (association)
Admitted, no hypothermia: S-CPR group, N (%) ResQCPR group	 21 (17.6) 42 (29.4)	 98 (82.4) 101 (70.6)	0.030[1]
Admitted, with therapeutic hypothermia: S-CPR group ResQCPR group	 26 (31.0) 33 (35.5)	 58 (69.0) 60 (64.5)	0.632[2]
Admitted, with or without therapeutic hypothermia: S-CPR group ResQCPR group	 47 (23.2) 75 (31.8)	 156 (76.8) 161 (68.2)	0.054[3]

[1] p-value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.94; 95% confidence interval = 1.035, 3.705.
[2] p-value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.23; 95% confidence interval = 0.625, 2.418.
[3] p-value shown is for Fisher's Exact Test (2-sided). Odds Ratio = 1.55; 95% confidence interval = 0.989, 2.428.

A total of 20 subjects in the S-CPR and 27 subjects in the ResQCPR groups were discharged from the hospital with poor neurological function as determined by a Cerebral Performance Category scale of ≤3. Those subjects with a poor CPC score who were treated with hospital therapeutic hypothermia plus ResQCPR had a higher likelihood of improving by 90 days after OHCA (64.3%) versus those treated with S-CPR and hypothermia (11.1%) (p=0.029).

Figure 8.8 Improvement from Poor Neurologic Function (CPC≥3) at Discharge to Favorable Neurologic Function (CPC≤2) at 90 Days (mITT)



	S-CPR without TH	S-CPR with TH	ACD+ITD without TH	ACD+ ITD with TH
CPC ≤2 at HD	24	30	43	32
CPC ≥ 3 at HD	11	9	13	14
Improved from CPC ≥ 3 at HD to CPC ≤2 at 90 days	3/11 (27.2%)	1/9 (11.1%)	3/13 (23.1%)	9/14 (64.3%)

Taken together, these observations support the conclusion that ResQCPR is neuro-protective, independent of TH. Without confirmed TH, survival with favorable neurologic function was nearly doubled with ResQCPR, compared with S-CPR: at hospital discharge, 29.4% versus 17.6% (p=0.030); and at 90 days, 26.3% (35/133) versus 16.2% (19/117) (p=0.065). In patients with poor neurologic function at hospital discharge, ResQCPR with TH resulted in a 6-fold improvement in neurologic function: by 90 days, 11.1% vs. 64.3%, p=0.029 (nominal unadjusted p-value) (**Figure 8.8**).

8.9.7.8 Frequency of Ventricular Fibrillation (VF) as the First Recorded Rhythm

VF was the first recorded rhythm in more subjects treated with ResQCPR (n=66) than S-CPR (n=40) in the mITT analysis population, although overall differences were not statistically significant between groups. An exploratory analysis was performed on all mITT subjects in VF who were not treated with bystander CPR to examine whether CPR treatment altered the frequency of VF, since 2 minutes of S-CPR or ResQCPR were delivered before the first rhythm analysis. The results demonstrated that a total of 106/459 (23.1%) subjects in the S-CPR and 164/484 (33.9%) in the ResQCPR group presented with VF as the first recorded rhythm in the absence of bystander CPR (OR 1.7, 95% CI [1.27, 2.30] p<0.001 (nominal unadjusted p-value). Of those, 21/455 (4.6%) in the S-CPR group survived to hospital discharge with favorable neurological function versus 43/482 (8.9%) in the ResQCPR group (OR 2.0, [1.15, 3.65] (p=0.009) (nominal unadjusted p-value). Thus, in the absence of bystander CPR, ResQCPR significantly increased the incidence of first recorded VF, return of spontaneous circulation and survival with mRS≤3. After propensity adjustment for witnessed arrest, age <67, gender, and public location, ResQCPR remained a significant predictor of an mRS≤3 (p= 0.02). We

conclude the incidence of VF as the first recorded rhythm may be influenced by the method of CPR delivered in subjects who did not receive bystander CPR.[105]

8.10 Safety Results

8.10.1 Adverse Events

The secondary safety endpoint of the study was the incidence rate of pre-specified major adverse events in the two study groups. This endpoint was evaluated using tests of non-inferiority of the rates of major adverse events in the investigational device group compared to the control group. The number and type of reported adverse events that were observed pre-hospital and up to the time of hospital discharge are shown in **Table 8.29** (mITT) and **Table 8.30** (ITT). There were no differences in overall major adverse event rates between the study groups, although occurrence of pulmonary edema was increased in the ResQCPR group in proportion to the overall increase in survivors treated with the study devices.

Table 8.29 Major Adverse Events through Hospital Discharge (mITT)[1]

Event	S-CPR (N= 813 subjects)	ResQCPR (N= 842 subjects)	p-value
Subjects with ≥1 pre-specified Major Adverse Event through hospital discharge **(Secondary Safety Endpoint[2])**	763 (93.8)	782 (92.9)	0.432
Death, through hospital discharge	729 (89.7)	735 (87.3)	0.144
Re-arrest	161 (19.8)	185 (22.0)	0.304
CVA/cerebral bleeding	3 (0.4)	2 (0.2)	0.682
Internal organ injury	0	1 (0.1)	1.000
Bleeding requiring transfusion or surgical intervention	3 (0.4)	7 (0.8)	0.343
Seizure	13 (1.6)	11 (1.3)	0.684
Rib/Sternal fracture	14 (1.7)	11 (1.3)	0.549
Pulmonary edema[3]	62 (7.6)	94 (11.2)	0.015

[1]Numbers shown are subjects with at least one report of the listed adverse event types. If multiple events of same type were reported, the event is only counted once per subject. Reports of deaths, re-arrest, seizure, and pulmonary edema in the field (e.g., pre-hospital) are also shown. All other adverse event types were assessed based on review of medical records for subjects transported to a hospital. There were no Major Adverse Events associated with device malfunctions, defects, or failures.

[2]Secondary safety endpoint: The rate of major adverse events in the ResQCPR group was found to be non-inferior to that in S-CPR group ($p < 0.0001$) within a non-inferiority margin of 5%.

[3]Data shown includes combined pre-hospital and in-hospital reports of pulmonary edema. Pulmonary edema was defined as any of the following: Pre-hospital reports of advanced airway filled with fluid ≥2 times; blood, mucous, fluid or other secretions in the airway; reports of pulmonary edema or pleural/pulmonary effusion on post-mortem examinations; and, for subjects transported to a hospital, in-hospital reports of pulmonary edema or pleural/pulmonary effusion confirmed on x-ray or CT scan. Pre-hospital pulmonary edema was reported in 22 patients (2.7%) in the S-CPR group, and in 29 patients (3.5%) in the ResQCPR group (p= 0.037).

Table 8.30 Major Adverse Events through Hospital Discharge (ITT)[1]

Event	S-CPR (N= 1201 subjects)	RESQCPR (N= 1269 subjects)	p-value
Subjects with ≥1 Major Adverse Event through hospital discharge	1129 (94.0)	1194 (94.1)	0.932
Death, through hospital discharge[2]	1074 (89.4)	1115 (87.9)	0.229
Re-arrest	230 (19.2)	260 (20.5)	0.420
CVA/cerebral bleeding	11 (0.9)	11 (0.9)	1.000
Internal organ injury	2 (0.2)	2 (0.2)	1.000
Bleeding requiring transfusion or surgical intervention	8 (0.7)	17 (1.3)	0.109
Seizure	19 (1.6)	23 (1.8)	0.349
Rib/Sternal fracture	23 (1.9)	18 (1.4)	0.349
Pulmonary edema[3]	96 (8.0)	143 (11.3)	0.006

[1]Numbers shown are subjects with at least one report of the listed adverse event types. If multiple events of same type were reported, the event is only counted once per subject. There were no Major Adverse Events associated with device malfunctions, defects, or failures.

2 Deaths in S-CPR group include two subjects (b)(6) and (b)(6) who were confirmed dead but it was unknown if the death occurred in-hospital or after discharge. Deaths in the ACD+ITD group include one subject (b)(6) who was confirmed dead but it was unknown if the death occurred in-hospital or after discharge.

There were no unanticipated adverse device effects. There was one reported serious unanticipated adverse event: death and pneumothorax in a subject treated with S-CPR. The CEC adjudicated the adverse event as unexpected/unanticipated.

8.10.2 Pulmonary Edema

The only statistically significant difference in adverse events between the two groups was the observation that more patients treated with ResQCPR had pulmonary edema. A post hoc analysis demonstrated that the presence of pulmonary edema did not adversely affect survival to hospital discharge with a mRS≤3, the primary study endpoint. As shown in **Table 8.31** and **Table 8.32,** these post-hoc analyses suggest that the presence of pulmonary edema in both the S-CPR and ResQCPR groups did not adversely affect the primary study outcome. It is also noted that there are good treatments when pulmonary edema does develop.

Table 8.31 Primary Endpoint and Pulmonary Edema in S-CPR Group (mITT)

		Pulmonary Edema AE		
		No	Yes	Total
mRS=<3	Count	39	8	47
	% within Pulmonary Edema AE	5.3%	13.1%	5.9%
mRS>=4	Count	700	53	753
	% within Pulmonary Edema AE	94.7%	86.9%	94.1%
Total	Count	739	61	800
	% within Pulmonary Edema AE	100.0%	100.0%	100.0%

p = 0.021 (Fisher's Exact Test, 2-sided)

Table 8.32 Primary Endpoint and Pulmonary Edema in ResQCPR Group (mITT)

		Pulmonary Edema AE		
		No	Yes	Total
mRS=<3	Count	59	16	75
	% within Pulmonary Edema AE	7.9%	17.0%	8.9%
mRS>=4	Count	685	78	763
	% within Pulmonary Edema AE	92.1%	83.0%	91.1%
Total	Count	744	94	838
	% within Pulmonary Edema AE	100.0%	100.0%	100.0%

p = 0.007 (Fisher's Exact Test, 2-sided)

8.11 Clinical Interpretation/Conclusions

This clinical trial represents a significant advance in the field of resuscitation. The results of the pivotal trial show that the treatment effect of the ResQCPR System on survival to hospital discharge with favorable neurologic function is superior to standard CPR (S-CPR), the best standard of care available in the United States today. There was a 52% increase in survival to hospital discharge with favorable neurologic function in subjects with an OHCA of presumed cardiac etiology treated with the ResQCPR System (75/838) compared with S-CPR (47/800) (p=0.019). The study results were robust. In the ITT population (n=2470), the effect of the ResQCPR system on survival to hospital discharge with favorable neurologic function was 35% higher than that observed with S-CPR (p=0.057). In addition, subgroup analysis based upon age, gender, first record rhythm, witnessed status, site of arrest, and 911 to EMS CPR time demonstrated a consistent benefit with ResQCPR. Consistent with these results, survival to one year was also 49% higher in the ResQCPR treatment group (p=0.030). One year after OHCA, greater than 95% of surviving subjects in both treatment groups had excellent neurological function, as determined by cognitive, functional, and quality of life testing. Further, subjects treated with the ResQCPR System and S-CPR had similar adverse event rates.

9 RISK/BENEFIT ANALYSIS

Cardiac arrest is a devastating event requiring immediate intervention if there is to be any possibility for survival. Approximately 1,000 people die from OHCA each day in the United States, making this epidemic one of the nation's leading causes of death. Despite 50 years of effort, survival rates from sudden cardiac arrest across the United States remains dismal. Data from the ResQTrial provides valid scientific evidence that the ResQCPR System is safe and effective and can be used to increase survival rates with favorable neurological outcomes above those achievable today with S-CPR. There are no alternative therapies to the ResQCPR System that have been approved for use by the FDA to increase neurologically intact survival from sudden cardiac arrest. The benefits of the ResQCPR System, which has been demonstrated to provide a significant increase in neurologically intact survival to hospital discharge and increased long-term survival up to one year, clearly outweigh the relatively low risks associated with this device.

9.1 Risks

The ResQCPR System is a very low-risk device. It is externally-applied during CPR to help improve circulation to the heart and brain and increase neurologically intact survival from sudden cardiac arrest. Increasing survival from sudden cardiac arrest introduces the potential risk that more survivors may not have good neurologic function. However, the clinical results from the ResQTrial demonstrated that the overall number of survivors increased with the ResQCPR System without an increase in the percentage of survivors with poor neurologic function.

Inherent in the use of any technology is the potential risk of device malfunction, incorrect use or a delay in treatment while the device is being deployed. The analysis of these risks for the ResQCPR System must consider that standard CPR is always available for the caregiver to provide. In the event of a delay in use of the ResQCPR System at the scene of a sudden cardiac arrest, device malfunction or incorrect use, the responder can always revert to standard CPR. The patient may not receive the full benefit of the ResQCPR in these circumstances, but there is no risk that the patient will receive a less effective treatment than he or she receives today as standard of care.

From a device design perspective, the ResQPump introduces the potential risk of using too much downward or upward force during chest compressions and decompressions, which could result in an increase in chest fractures and organ damage, or not enough downward force, which could reduce the forward blood flow generated with this technology. The device has both a visual force gauge that gives feedback on applied compression and decompression forces and a metronome to give feedback on the proper rate of compression and decompressions. The design of the ResQPOD introduces the risk of occluding the airway should a subject regain a pulse and spontaneous respiratory effort. This risk is mitigated by a safety check valve inside the device that allows for spontaneous inspiration.

The safety data provided by the ResQTrial demonstrated consistency across the patient population and raised no unique concerns with the ResQCPR System. The only adverse event found in a higher proportion of ResQCPR patients was pulmonary edema. While the occurrence

of pulmonary edema was found to be higher with the ResQCPR System, it did not affect the benefits associated with ResQCPR on the primary study endpoint, survival to hospital discharge with good neurological function. From a risk-benefit standpoint, the benefit of surviving a sudden cardiac arrest outweighs the risk of having treatable pulmonary edema.

Finally, the risk profile of the ResQCPR System will be reduced further through a robust training program for all users of the device. This training program has been developed based upon the experience gained from training nearly 5,000 medics during the ResQTrial.

9.2 Benefits

The ResQCPR System has a well-established mechanism of action for improving blood flow to the brain and other vital organs during sudden cardiac arrest. It is designed to improve CPR physiology by lowering intrathoracic pressure, enhancing venous return to the heart, and increasing cardiac output and blood flow to vital organs during CPR.

In addition to the physiologic benefit, the ResQCPR System also incorporates feedback mechanisms to help guide high-quality CPR. This includes a force gauge to provide feedback on compression/decompression force and metronomes to guide the timing of compressions and ventilations. This is important since the effectiveness of CPR can vary significantly based on compression rate, compression depth and timing of ventilation.

The ResQTrial demonstrated that the ResQCPR System can be efficiently deployed in the pre-hospital basic life support setting. The average time to device deployment upon arrival at the scene by the caregiver for all subjects without an EMS witnessed arrest and randomized to ResQCPR was less than 45 seconds. This is important since early intervention during sudden cardiac arrest provides the greatest opportunity for survival.

The ResQTrial was a robust clinical study funded and overseen by the NIH. Despite being a challenging study because of the emergency setting and exception to informed consent process, the Company was able to conduct the study under an approved IDE and in compliance with FDA guidance documents, and to obtain primary outcome data on 99% of the over 1600 subjects. ResQTrial oversight was provided by an independent DSMB and CEC.

A total of 1,655 subjects enrolled in the pivotal trial met criteria for the mITT study population and were evenly distributed between the S-CPR and ResQCPR System study arms. Differences in the rates of survival to hospital discharge with favorable neurological function were significantly higher in the ResQCPR study arm: there was a relative 52% increase in survival with favorable neurological outcomes (5.9% [47/800] vs 8.9% [75/838]) (p=0.019). In addition, there were 49 % more survivors one year after cardiac arrest in the ResQCPR treatment group (74/840 with ACD+ITD versus 48/813 with S-CPR, p=0.03). Among those who survived in both groups, there was no evidence of diminished neurological function. There was also a benefit in the entire ITT population. For all 2,470 non-traumatic OHCA subjects in the ITT population randomized in the pivotal phase of the study, 6.0% survived to hospital discharge with favorable neurological function after treatment with S-CPR versus 8.0% in the ResQCPR System group (p=0.057). This included subjects with non-cardiac etiologies. The benefit of the ResQCPR

System devices in terms of survival with satisfactory neurological function was observed at all time points in the study, across study sites, and regardless of age and gender. In addition, several post-hoc analyses were performed to further assess the effectiveness and the consistency of the results from the ResQTrial. These analyses are included in **Section 8.9.5.3** and help demonstrate the consistent benefit achieved by the ResQCPR System, ranging from 19.4% to 60.7%, regardless of the analysis population, subpopulation, or assumptions made in the analyses.

If the device were approved and were adopted widely, based on the results of the ResQTrial, the ResQCPR System would present an opportunity to save thousands more lives in the United States per year in the pre-hospital sudden cardiac arrest population.

9.3 Conclusions

In summary, the positive and consistent clinical results from the ResQTrial, regardless of how the data are analyzed, the non-invasive mechanism of action of the ResQCPR System, the safety profile of the device combination, and the extraordinarily high mortality rates associated with OHCA today provide a compelling risk-benefit profile for use of the ResQCPR System to increase survival with favorable neurological function in patients with non-traumatic cardiac arrest.

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11 APPENDIX 1 Summary of Representative Clinical Trials Comparing Standard CPR (S-CPR) to ACD-CPR Alone

Table 11.1 Major Clinical Trials Comparing Standard CPR (S-CPR) to ACD-CPR Alone

Journal Citation	Design	S-CPR (n)	ACD-CPR (n)	Endpoints	Results	p-value; Odds Ratio (95% CI)
[106]Shultz et al. Circulation 1994; 89(2):684-693.	S-CPR vs. ACD-CPR Randomized, crossover; in-hospital	21		Calculated coronary perfusion pressure	Compression S-CPR: 17.9 ± 8.2 mmHg, ACD: 21.5 ± 9.0 mmHg Decompression S-CPR: 18.5 ± 6.9 mmHg ACD: 21.9 ± 8.7 mmHg	p < 0.02 p < 0.02
z[107]Cohen et al. JAMA 1992; 267(21):2916-2923	S-CPR vs. ACD-CPR Randomized, controlled, crossover	10		$ETCO_2$	S-CPR: 4.3 ± 3.8 mmHg ACD: 9.0 ± 3.9 mmHg	p < 0.0001
				Systolic arterial pressure	S-CPR: 52.5 ± 14.0 mmHg ACD: 88.9 ± 24.7 mmHg	p < 0.003
				Velocity time integral	S-CPR: 7.3 ± 2.6 cm ACD: 17.5 ± 5.6 cm	p < 0.0001
				Diastolic myocardial filling time	S-CPR: 0.23 ± 0.09 seconds ACD: 0.37 ± 0.12 seconds	p < 0.004
[108]Lurie et al. JAMA 1994; 271(18):1405-1411	S-CPR vs. ACD-CPR Prospective, randomized, parallel-group; out-of-hospital	77	53	ROSC	S-CPR: 31% ACD: 45%	p < 0.1
				ICU admission (downtime <10 minutes)	S-CPR: 33% ACD: 59%	p < 0.02
[109]Mauer et al. Resuscitation 1999; 41(3):249-256	S-CPR vs ACD-CPR Combined analysis of randomized, prospective studies; out-of-hospital	1456	1410	One-hour survival	S-CPR: 20.6% ACD: 23.8	p < 0.05 (0.695-0.99)
[69]Plaisance et al. N Engl J Med 1999; 341(8):569-575	S-CPR vs. ACD-CPR Prospective randomized; out-of-hospital	377	373	1° Survival at one year	S-CPR: 2% ACD: 5%	p = 0.03
	S-CPR vs.	In-	405	Survival to one hour	S-CPR: 35.1%	p = 0.89

Journal Citation	Design	S-CPR (n)	ACD-CPR (n)	Endpoints	Results	p-value; Odds Ratio (95% CI)
[75]Stiell et al. JAMA 1996; 275(18):1417-1423	ACD-CPR Randomized, controlled, blinded; out-of-hospital and in-hospital	hospital 368			ACD: 34.6%	
				Survival to hospital discharge	S-CPR: 11.4% ACD: 10.4%	p = 0.64
				Mini-mental state examination (median score)	S-CPR: 37 ACD: 37	p = NS
		Out-of-hospital 510	501	Survival to one hour	S-CPR: 16.5% ACD: 18.2%	p = 0.48
				Survival to hospital discharge	S-CPR: 3.7% ACD: 4.6%	p = 0.49
				Mini-mental state examination (median score)	S-CPR: 35 ACD: 35	p = NS
[110]Baubin et al. Resuscitation 1999; 43(1):9-15	ACD-CPR Prospective study; post-mortem	n/a	38	Sternal fractures	Male: 2/20 Female: 9/17	p = 0.008
				Sternal fractures	Average age Sternal fracture: 71.5 ± 11.8 years No sternal fracture: 77.9 ± 11.8 years	p = 0.008
				Sternal/rib fractures	Max compression force Sternal fracture: 450 ± 78 *N* No sternal fracture: 405 ± 32 *N*	p = 0.048
[111]Baubin et al. Resuscitation 1999; 41(1):33-38	S-CPR by first tier vs.ACD-CPR by first tier Prospective, randomized; out-of-hospital	42	33	Rib fractures in patients undergoing autopsy	S-CPR: 11/20 ACD: 13/15	p < 0.05
				Sternal fractures in patients undergoing autopsy	S-CPR: 6/20 ACD: 14/15	p < 0.005

12 APPENDIX 2 Long-Term Outcomes Assessed by Multiple Neurological Assessment Tools

Table 12.1 CPC Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
CPC ≤ 2 at hospital discharge	54	75	0.099
CPC ≤ 2 30 days after OHCA	52	69	0.158
CPC ≤ 2 90 days after OHCA	47	72	0.029
CPC ≤ 2 365 days after OHCA	43	62	0.086

Table 12.2 CPC Scores at All Follow-ups (ITT)

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
CPC ≤ 2 at hospital discharge	78	102	0.141
CPC ≤ 2 30 days after OHCA	72	84	0.509
CPC ≤ 2 90 days after OHCA	66	88	0.135
CPC ≤ 2 365 days after OHCA	56	76	0.129

Table 12.3 OPC Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
OPC ≤ 2 at hospital discharge	47	68	0.082
OPC ≤ 2 30 days after OHCA	48	62	0.277
OPC ≤ 2 90 days after OHCA	44	69	0.032
OPC ≤ 2 365 days after OHCA	42	62	0.068

Table 12.4 OPC Scores at All Follow-ups (ITT)

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
OPC ≤ 2 at hospital discharge	70	91	0.193
OPC ≤ 2 30 days after OHCA	66	74	0.728
OPC ≤ 2 90 days after OHCA	62	83	0.171
OPC ≤ 2 365 days after OHCA	54	73	0.146

Table 12.5 HUI3 Scores at All Follow-ups (mITT)[1]

	S-CPR (n=813)	RESQCPR (n=842)	p-value
HUI3 at hospital discharge	17.81 ± 10.61	17.01 ± 8.93	0.646
HUI3 30 days after OHCA	13.45 ± 6.24	13.94 ± 6.81	0.685
HUI3 90 days after OHCA	11.86 ± 3.89	12.35 ± 5.98	0.636
HUI3 365 days after OHCA	12.49 ± 4.45	12.10 ± 6.00	0.736

[1]HUI results are mean scores from subjects for which the entire assessment was completed

Table 12.6 HUI3 Scores at All Follow-ups (ITT)[1]

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
HUI3 at hospital discharge	19.47 ± 11.35	17.49 ± 8.71	0.201
HUI3 30 days after OHCA	16.10 ± 9.78	15.08 ± 7.71	0.453
HUI3 90 days after OHCA	14.94 ± 9.03	12.98 ± 6.54	0.133
HUI3 365 days after OHCA	13.85 ± 7.34	12.45 ± 5.87	0.241

[1]HUI results are mean scores from subjects for which the entire assessment was completed

Table 12.7 DRS Scores at All Follow-ups (mITT)[1]

	S-CPR (n=813)	RESQCPR (n=842)	p-value
DRS 30 days after OHCA	3.57 ± 5.31	4.48 ± 6.27	0.381
DRS 90 days after OHCA	1.91 ± 3.41	2.58 ± 5.22	0.440
DRS 365 days after OHCA	1.39 ± 3.12	2.19 ± 5.68	0.412

[1]DRS results are mean scores from subjects for which the entire assessment was completed. DRS scores are divided into 9 categories, loss of neurologic function defined as follows: none (score of 0), mild (score of 1), partial (score of 2-3), moderate (score of 4-6), moderately severe (score of 7-11), severe (score of 12-16), extremely severe (score of 17-21), vegetative state (score of 22-24), and extreme vegetative state (score of 25-29)

Table 12.8 DRS Scores at All Follow-ups (ITT)[1]

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
DRS 30 days after OHCA	5.54 ± 8.07	5.54 ± 7.32	0.997
DRS 90 days after OHCA	4.49 ± 7.90	3.59 ± 6.53	0.424
DRS 365 days after OHCA	2.46 ± 5.47	2.91 ± 6.09	0.654

[1]DRS results are mean scores from subjects for which the entire assessment was completed. DRS scores are divided into 9 categories, loss of neurologic function defined as follows: none (score of 0), mild (score of 1), partial (score of 2-3), moderate (score of 4-6), moderately severe (score of 7-11), severe (score of 12-16), extremely severe (score of 17-21), vegetative state (score of 22-24), and extreme vegetative state (score of 25-29)

Table 12.9 Trail Making Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
Trail Making A 90 days after OHCA	42.53 ± 27.03	49.80 ± 34.12	0.290
Trail Making A 365 days after OHCA	49.56 ± 43.37	47.10 ± 27.26	0.772
Trail Making B 90 days after OHCA	83.09 ± 40.05	108.62 ± 50.46	0.017
Trail Making B 365 days after OHCA	87.48 ± 43.12	100.54 ± 64.47	0.368

Table 12.10 Trail Making Scores at All Follow-ups (ITT)

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
Trail Making A 90 days after OHCA	50.54 ± 42.16	54.48 ± 40.23	0.612
Trail Making A 365 days after OHCA	48.95 ± 41.69	50.96 ± 32.54	0.799
Trail Making B 90 days after OHCA	87.56 ± 49.17	112.74 ± 60.73	0.024
Trail Making B 365 days after OHCA	85.75 ± 38.87	111.79 ± 75.23	0.055

Table 12.11 BDI Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
BDI 90 days after OHCA	4.80 ± 3.91	6.51 ± 6.77	0.098
BDI 365 days after OHCA	5.23 ± 6.29	5.46 ± 5.93	0.862

Table 12.12 BDI Scores at All Follow-ups (ITT)

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
BDI 90 days after OHCA	6.17 ± 6.54	7.09 ± 6.90	0.426
BDI 365 days after OHCA	6.52 ± 7.25	5.87 ± 6.04	0.599

Table 12.13 MPAI Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
MPAI 90 days after OHCA	13.23 ± 22.51	13.94 ± 24.39	0.874

Table 12.14 MPAI Scores at All Follow-ups (ITT)

MPAI 90 days after OHCA	16.14 ± 23.10	15.15 ± 25.30	0.807

Table 12.15 QOLS Scores at All Follow-ups (mITT)

	S-CPR (n=813)	RESQCPR (n=842)	p-value
QOLS 365 days after OHCA	2.02 ± 0.79	2.09 ± 0.99	0.706

Table 12.16 QOLS Scores at All Follow-ups (ITT)

	S-CPR (n=1201)	RESQCPR (n=1269)	p-value
QOLS 365 days after OHCA	2.05 ± 0.98	2.20 ± 1.06	0.407

13 APPENDIX 3 Additional FDA Post Hoc Analyses

Several additional post-hoc analyses have been performed by the FDA to examine the robustness of the treatment results. These post-hoc analyses are relevant given the unique nature of conducting research in the out-of-hospital sudden cardiac arrest environment, the heterogeneous composition of the sudden cardiac arrest population, the inclusion/exclusion criteria for the study and the sensitivity of the statistical results. Further, these post-hoc analyses are pertinent given that the post-marketing experience will involve use of the ResQCPR System in all sudden non-traumatic cardiac arrest patients, regardless of the underlying arrest etiology.

These additional post-hoc analyses demonstrate a consistent improvement in outcomes with the use of the ResQCPR System, regardless of the analysis population, subpopulation, or assumptions made in the analyses, as shown by the percent difference in rate of survival to hospital discharge with MRS ≤ 3 between arms, ranging from 9% to 60%.

Medication/Drug ODs

To investigate the potential impact of these 163 excluded overdose subjects on the primary analysis results, FDA added them to the mITT cohort. See Table 13.1.

Table 13.1 Survival to Hospital Discharge with MRS ≤ 3, mITT plus 163 drug overdose subjects (Complete Case) (By FDA)

Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
S-CPR vs. ACD-ITD	6.59% (57/865), 13 missing	8.98% (84/935), 5 missing	36.3%
First 1400 subjects	6.82% (47/689)	9.46% (66/698)	38.7%
CHW method	6.59% (57/865)*	8.98% (84/935)*	36.3%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).

Late Adjudication

There were 28 subjects who appeared to be removed from the mITT analysis based on late adjudication of cardiac arrest etiology. To investigate the potential impact of these 28 subjects, FDA added them to the mITT analysis population as shown in **Table 13.2**.

Table 13.2 Survival to Hospital Discharge with MRS ≤ 3, mITT plus 28 delayed adjudicated subjects (Complete Case) (By FDA)

Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
S-CPR vs. ACD-ITD	6.20% (50/806)	8.84% (76/860)	42.6%
First 1400 subjects	6.48% (44/679)	9.17% (65/709)	41.5%
CHW method	6.20% (50/806)*	8.84% (76/860)*	42.6%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).

Randomization Errors

To investigate the potential impact of randomization errors, as-treated analyses were performed. The following methods were employed:

Method 1

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with a least "1" device, either ACD, ITD, or both (n = 782+32 = 814)

Method 2

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- ACD-ITD subjects included if they received CPR with both ACD and ITD devices (n = 782)

Method 3

- All Subjects, regardless of randomization assignment, re-classified as having received s-CPR with "0" devices (n=803+28=831) or having received ACD-ITD with "2" devices (n782+5=787).

Method 4

- s-CPR subjects included if they received CPR with "0" devices (n = 803)
- all ACD-ITD subjects, irrespective of devices actually used (n=782+32+28=842).

Table 13.3 Survival to Hospital Discharge with MRS ≤ 3, As-Treated Analysis (Complete Case) (By FDA)

Approach	Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
Original planned 1400 subjects	Method 1	6.07% (41/675)	8.50% (58/682)	40.0%
	Method 2	6.07% (41/675)	8.24% (54/655)	35.7%
	Method 3	6.74% (47/697)	8.19% (54/659)	21.5%
	Method 4	6.07% (41/675)	9.09% (64/704)	49.8%
CHW approach	Method 1	5.95% (47/790) *	8.26% (67/811) *	38.8%
	Method 2	5.95% (47/790) *	8.09% (63/779) *	36.0%
	Method 3	6.73% (55/817) *	8.04% (63/784) *	19.5%
	Method 4	5.95% (47/790) *	8.95% (75/838) *	50.4%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).

Unobtainable Primary Endpoint Data

To determine the potential impact of missing primary endpoint data on the study results, FDA performed a best case analysis.

Table 13.4 Survival to Hospital Discharge with MRS ≤ 3, Best Case Analysis for as-treated population (By FDA)

Approach	Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
First enrolled 1400 subjects	Method 1	5.99% (41/684)	8.77% (60/684)	46.4%
	Method 2	5.99% (41/684)	8.52% (56/657)	42.2%
	Method 3	6.65% (47/707)	8.47% (56/661)	27.4%
	Method 4	5.99% (41/684)	9.48% (67/707)	58.3%
Inverse Normal	Method 1	5.85% (47/803)*	8.60% (70/814)*	47.0%

Method (CHW)	Method 2	5.85% (47/803)*	8.44% (66/782)*	44.3%
	Method 3	6.62% (55/831)*	8.39% (66/787)*	26.7%
	Method 4	5.85% (47/803)*	9.38% (79/842)*	60.3%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).

Medication/Drug Overdose Patients

To investigate the impact of excluded overdose subjects on the analysis results, FDA added the 163 medication/drug overdose subjects in the mITT and as-treated analyses.

Table 13.5 Survival to Hospital Discharge with MRS ≤ 3, mITT/as-treated plus drug overdose subjects (Complete Case) (by the FDA)

Analysis Population	Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
mITT	All S-CPR vs. ACD-ITD	6.59% (57/865)	8.98% (84/935)	36.3%
	First 1400 subjects	6.82% (47/689)	9.46% (66/698)	38.7%
	CHW method	6.59% (57/865)*	8.98% (84/935)*	36.3%
As-Treated Method 1	All S-CPR vs. ACD-ITD#	6.67% (57/855)	8.30% (75/904)	24.4%
	First 1400 subjects	6.91% (47/680)	8.88% (60/676)	28.5%
	CHW method	6.67% (57/855)*	8.30% (75/904)*	24.4%
As-Treated Method 2	All S-CPR vs. ACD-ITD#	6.67% (57/855)	8.20% (71/866)	22.9%
	First 1400 subjects	6.91% (47/680)	8.63% (56/649)	24.9%
	CHW method	6.67% (57/855)*	8.20% (71/866)*	22.9%
As-Treated Method 3	All S-CPR vs. ACD-ITD#	7.45% (66/886)	8.15% (71/871)	9.4%
	First 1400 subjects	7.55% (53/702)	8.58% (56/653)	13.6%
	CHW method	7.45% (66/886)*	8.15% (71/871)*	9.4%
As-Treated Method 4	All S-CPR vs. ACD-ITD#	6.67% (57/855)	8.98% (84/935)	34.6%

	First 1400 subjects	6.91% (47/680)	9.46% (66/698)	36.9%
	CHW method	6.67% (57/855)*	8.98% (84/935)*	34.6%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).

Late Adjudication

To investigate the impact on the study conclusion of the 28 subjects removed from the mITT analysis based on late adjudication of cardiac arrest etiology, FDA added these 28 subjects to the mITT and as-treated analyses:

Table 13.6 Survival to Hospital Discharge with MRS ≤ 3, mITT plus 28 delayed adjudicated subjects (Complete Case) (by the FDA)

Analysis Population	Method	S-CPR	ACD-ITD	Relative % increase from S-CPR to ResQCPR
mITT	S-CPR vs. ACD-ITD	6.20% (50/806)	8.84% (76/860)	42.6%
	First 1400 subjects	6.48% (44/679)	9.17% (65/709)	41.5%
	CHW method	6.20% (50/806)*	8.84% (76/860)*	42.6%
As-Treated Method 1	S-CPR vs. ACD-ITD#	6.28% (50/796)	8.17% (68/832)	30.1%
	First 1400 subjects	6.57% (44/670)	8.59% (59/687)	30.7%
	CHW method	6.28% (50/796)*	8.17% (68/832)*	30.1%
As-Treated Method 2	S-CPR vs. ACD-ITD#	6.28% (50/796)	8.03% (64/797)	27.9%
	First 1400 subjects	6.57% (44/670)	8.35% (55/659)	27.1%
	CHW method	6.28% (50/796)*	8.03% (64/797)*	27.9%
As-Treated Method 3	S-CPR vs. ACD-ITD#	7.04% (58/824)	7.98% (64/802)	13.4%
	First 1400 subjects	7.23% (50/692)	8.30% (55/663)	14.8%
	CHW method	7.04% (58/824)*	7.98% (64/802)*	13.4%
As-Treated Method 4	S-CPR vs. ACD-ITD#	6.28% (50/796)	8.84% (76/860)	40.8%
	First 1400 subjects	6.57% (44/670)	9.17% (65/709)	39.6%

	CHW method	6.28% (50/796)*	8.84% (76/860)*	40.8%

*: This rate is just the overall event rate by ignoring stage 1 (before the interim look) and stage 2 (after the interim look).